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TITLE: Hypo-Fractionated Conformal Radiation Therapy to the Tumor Bed After Segmental Mastectomy

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13. Abstract *(Maximum 200 Words)* *(abstract should contain no proprietary or confidential information)*

The current trial tests a regimen of conformal hypo-fractionated radiotherapy (5 fractions) directed to the original tumor bed with margins in a selected subset of post-menopausal women with breast cancer with a very low risk for local recurrence elsewhere in the breast. We are currently reporting the feasibility results and DVH analysis of the first 29 patients accrued. After planning CT is conducted in the prone position the breast tissue and tumor bed are contoured on a 3D planning system and a 2 cm margin added to determine the PTV. A plan is generated to treat the PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95 % isodose surface in 5 fractions over ten days weeks to a total dose of 30 Gy. All patients appeared to tolerate treatment very well. DVH varied based on the position of the original tumor bed and the size of the breast. In most cases it was possible to successfully plan and treat a quadrant of the breast with parallel opposed tangent fields without exceeding 50% of the dose to 50% of the breast volume. We continue accrual as planned, to a total of 99 patients.

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INTRODUCTION:

Since in a selected subset of post-menopausal women with breast cancer there is a very low risk for local recurrence elsewhere in the breast, a regimen of conformal hypo-fractionated radiotherapy (5 fractions in 2 weeks) directed to the original tumor bed with margins, could generates local control rates and cosmetic results equivalent to those achieved by conventional post-operative radiotherapy (30 fractions over 6 weeks) while being much more convenient and economical.

The specific aims of this IDEA grant are:

1. To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers.
2. To explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation.
3. To prospectively assess the role of circulating TGF-□1pre-treatment as a marker for post-treatment fibrosis.
4. To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams

BODY:

An NYU–IRB approved protocol testing the research hypothesis of this study has been actively recruiting patients since October 2000, with independent funding from those allocated by the current award.

The study expects to accrue a total of 99 patients in 3 years.

We are hereby reporting the preliminary results obtained by studying the first 29 patients accrued, since the modifications to the protocol and the consent required by the DOD and included in the currently open protocol were minor and have not modified the research component of the trial. The subsequent 70 patients accrued will be consented with the reviewed and corrected active protocol, and will sign the reviewed consent that reflects the minor changes required by the DOD. While the clinical results and conclusions will be merged, care will be taken to specify in any presentation or publication the separate source of support for the two consecutive patients cohorts.

With regard to Task 1 and 2 of the approved statement of work: (year 1-4)

"To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers, and to explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation."

The current study is offered only to eligible post-menopausal women who have refused to undergo conventional six-weeks radiation after segmental mastectomy. A total of 32 patients refused to undergo conventional radiation therapy and were also eligible to the trial; 29/32 chose to enter the study, with an acceptance rate of 90%.

At the time of the current report 29 patients have accrued: only one patient has interrupted treatment after receiving the first fraction of radiation. No detectable toxicity

was associated with treatment and the patient refused to return for further treatment despite numerous efforts to convince her to continue. This patient remains in communication with her primary doctor and she is reported to be NED a year later.
Among the 28 patients who have completed treatment no recurrence have occurred: median follow up is 10 months. All patients appear to tolerate treatment very well with only mild discomfort reported when lying prone for planning and treatment.
In addition, follow-up of the pilot cohort of nine patients treated 5 years ago at USC, has shown no recurrences in this small group of patients: the data is reported in a manuscript published in the January/2002 issue of Radiology (ref.1.copy attached in appendix).

During this first phase of the trial we have focused on two tasks:

1) designing a more comfortable and reliable treatment table that can enable geriatric breast cancer patients to comfortably withstand the treatment in prone position.

As a result of a partnership with one of our breast cancer survivor/advocate who is an architect, a new, much more comfortable table for prone imaging and treating was designed (designing and engineering was generously donated by our partner-advocate) and built, as per the attached digital photo (see appendix). The table is now ready for validation and testing to be compared to our previous table (2).

2) developing preliminary **physics data about dose volume histogram (DVH) analysis** in the studied population.

Much of our initial research effort has been spent in studying geometric and anatomic issues of the tested technique and their dosimetric implications.
As described in the original proposal the breast tissue and tumor bed, identified at CT as the post-surgical cavity, are contoured on a 3D planning system (Varian Somavision/CadPlan) and a 2 cm margin added to determine the PTV. A plan was generated in the attempt to treat the entire PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95 % isodose surface in 5 fractions over ten days weeks. to a total dose of 30 Gy.
Currently 29 patients have completed treatment: median age is 68 (range 54-87). Average tumor diameter is 0.9 cm (range 0.2-1.5). Except for grade 1 erythema in 5/26 (25%) no other acute toxicity was detected. Planning in the prone position was feasible in all patients. The predominant technique for treatment was a pair of parallel-opposed tangents. This arrangement assured good coverage given the constraints imposed by the PTV and its relationship to the table. We found heterogeneity of DVH based on the position of the original tumor bed and the size of the breast. For the entire group the volume of breast tissue included by the 95% isodose ranged between 15% to 46%. Six of the patients received greater than 50% of the dose to 50% of the breast. Five of the patients treated had less than 25% of the breast tissue contained within the prescription isodose surface. In all patients volumes of heart and lung included in any of the treatment fields were clinically insignificant.
In conclusion, these preliminary data confirm in a larger number of patients that in most cases it is possible to successfully plan and treat a quadrant of the breast without

exceeding 50% of the dose to 50% of the breast volume. Although the intent was to be able to treat the breast tissue completely from beneath the table, portions of the PTV were often superior to the table. Alterations in the table design (like those applied to our recently completed new table) might improve the current dosimetric findings. Similar to the results in our pilot study this approach appears to be well tolerated with only mild acute side effects. Longer follow-up is required to assess efficacy and cosmesis.

Task 3: (year 1-4)
To prospectively assess the role of circulating TGF-□1pre-treatment as a marker for post-treatment fibrosis.

As planned, patients were seen once/week during treatment and once two weeks after. Thereafter they will be seen in follow up every 3 months for the first year and every six months for the following five years. At each visit, physical exam to detect clinical recurrence was performed and mammography films (once/year) were reviewed. The data has been regularly accrued and a copy of the Oracle forms specifically developed for data collection in this study is attached.

Task 4: (year 1-2)
To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams.

We had planned to establish the accuracy in target definition by ultrasound imaging and to compare it to CT imaging. Since funding for the acquisition of the US device was obtained only six month ago, only CT imaging was used for the first 29 patients accrued to the trial.
We plan to soon initiate the parallel US evaluation of target volume.

KEY RESEARCH ACCOMPLISHMENTS:

1. feasibility is demonstrated in the first 29 patients
2. dosimetric findings obtained in the first 29 patients appear to confirm our predictions.
3. optimal patient accrual, with an acceptance rate of 90% among patients who refused the initial recommendation for conventional six weeks of post-segmental mastectomy fractionated radiotherapy

REPORTABLE OUTCOMES:

Since the award was received the study has been presented by the P.I. at one international and two national conferences (both CME approved):

-IV Madrid Breast Cancer Conference: changes in the treatment of breast cancer. Madrid June 7-9, 2001

-Mayo Clinic Amelia Island Oncology Review Course
August 15-18, 2001

- Manhattan Breast Cancer Society
January 17, 2002

CONCLUSIONS:

The current trial has shown to be feasible and well tolerated. The encountered acceptance rate is 90% in the studied population and the accrual is close to the expected target (29/31).
Preliminary dosimetric findings encourage us to continue especially in view of the excellent tolerability of this approach. While no patient has recurred at this time, the planned one-year of minimum follow up for the first 31 patients has not been reached yet. The study continues as planned and approved.

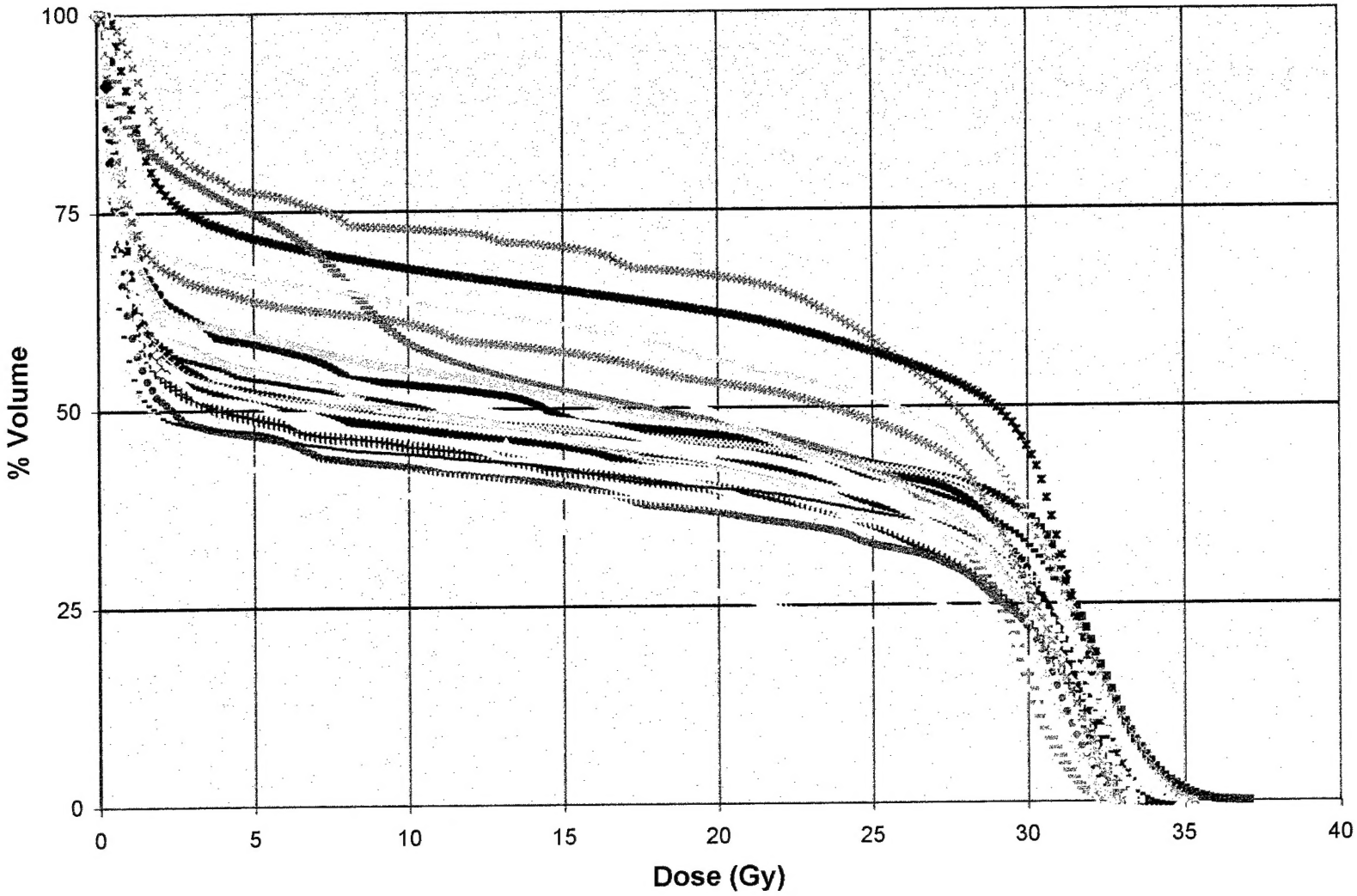
REFERENCES:

1) Formenti SC, et al Radiology. 2002 Jan;222(1):171-8
2) Joszef G et al Medical Physics 27(5): 1005-10 2000

APPENDICES:

1. DVH graph
2. copy of the manuscript
3. copy of Oracle database forms
4. Digital picture of the new table

Dose-Volume Histograms of Breast Tissue for Patients Receiving Partial Breast Irradiation



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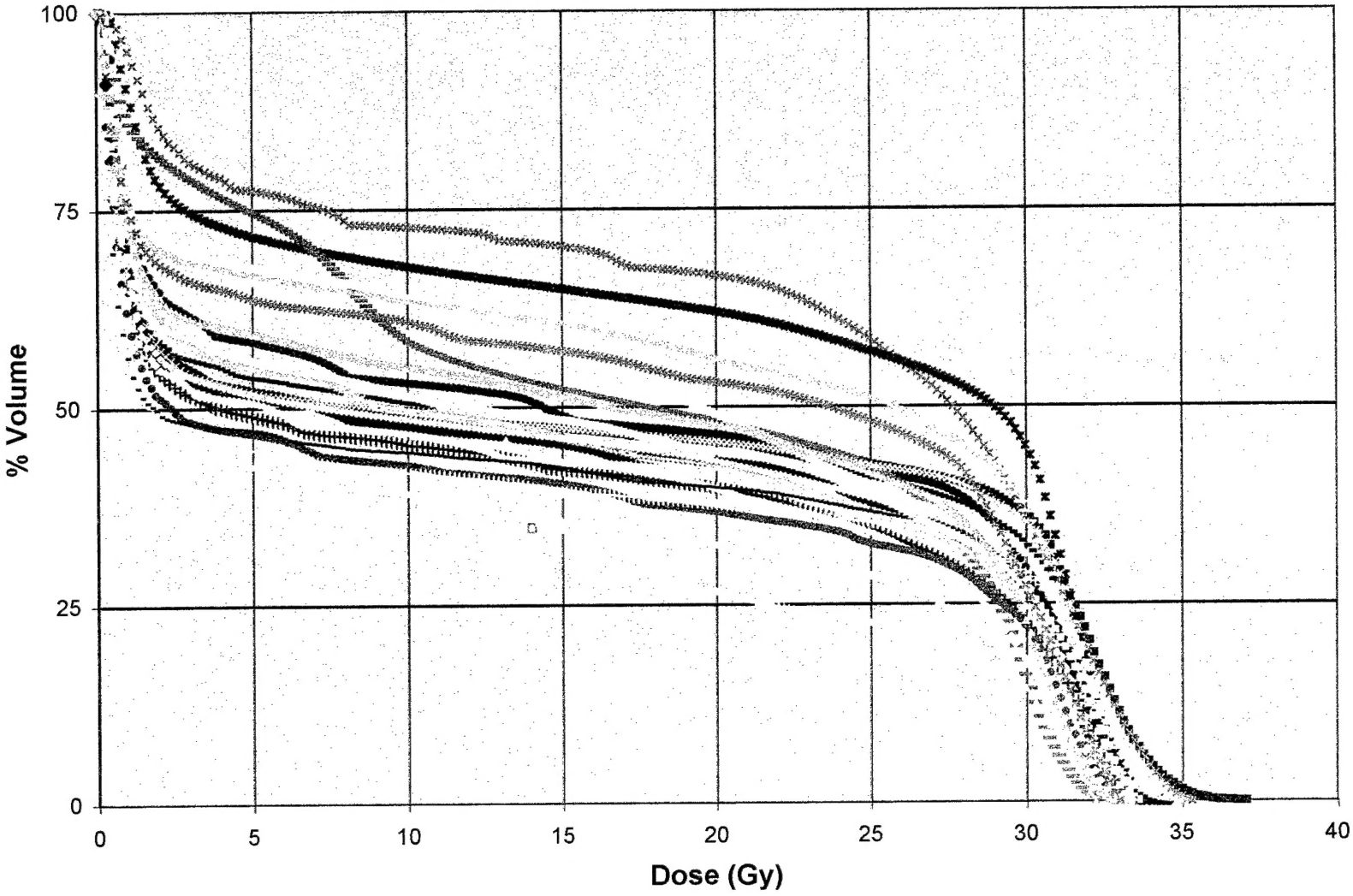

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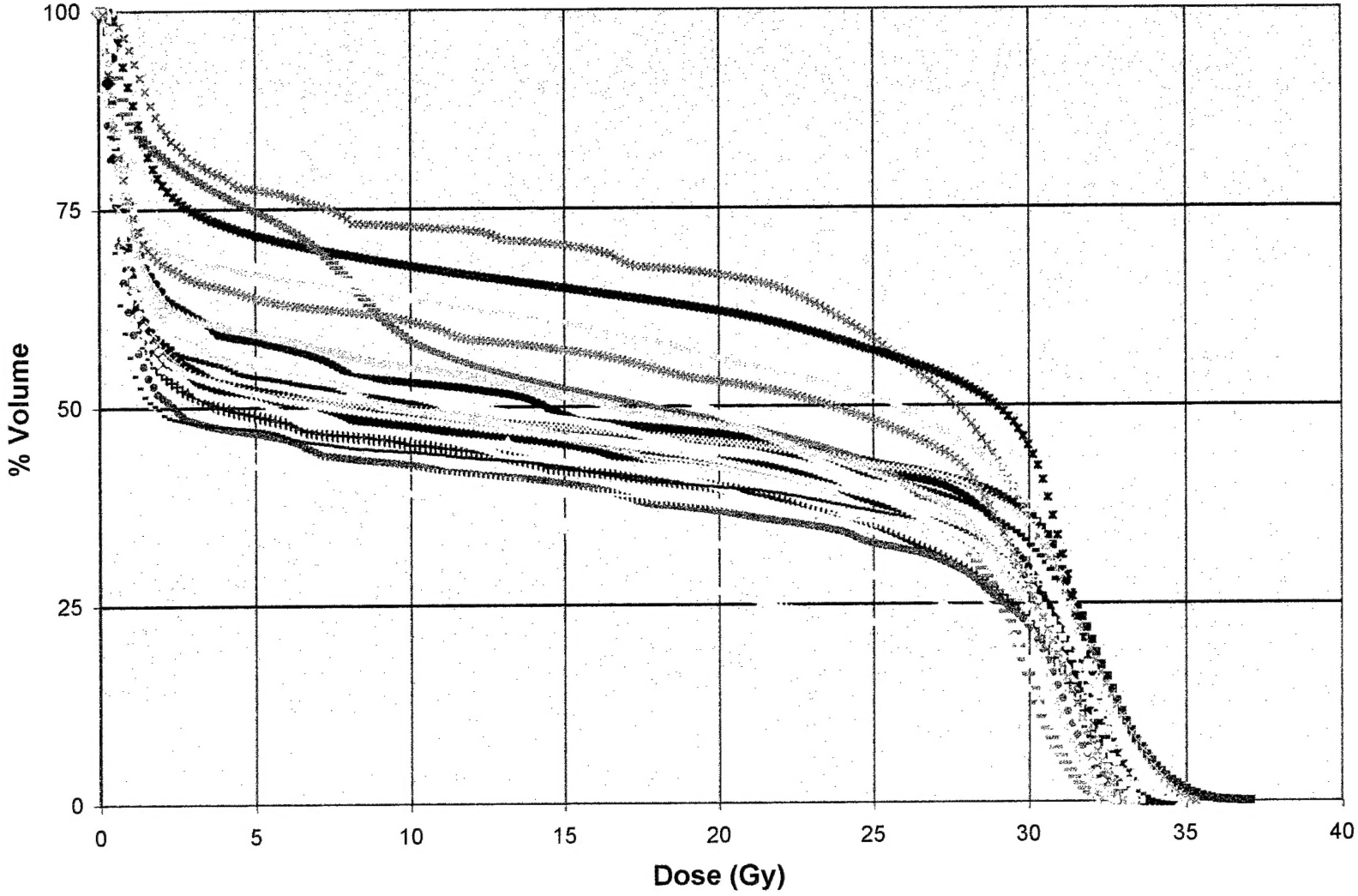

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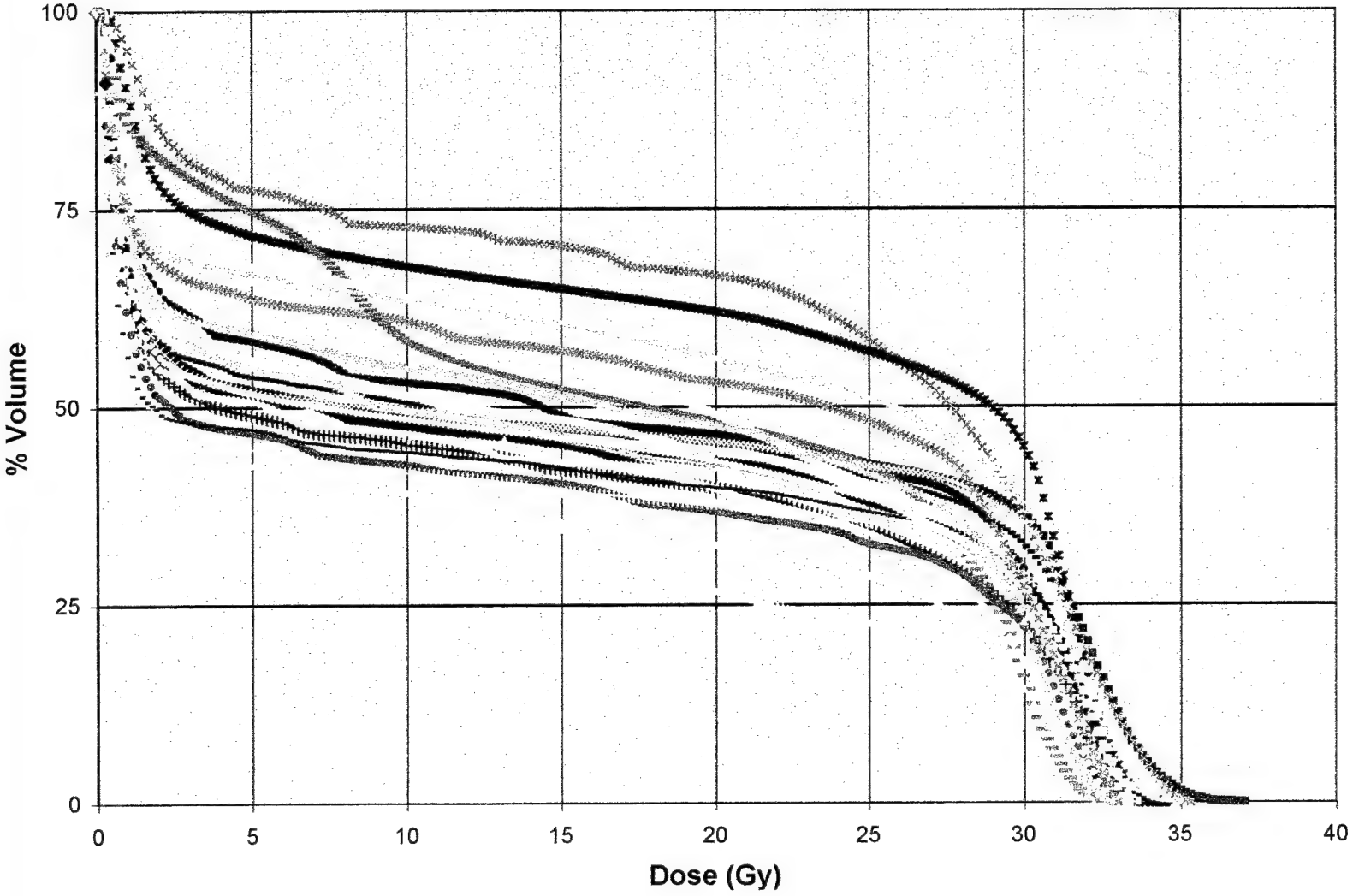
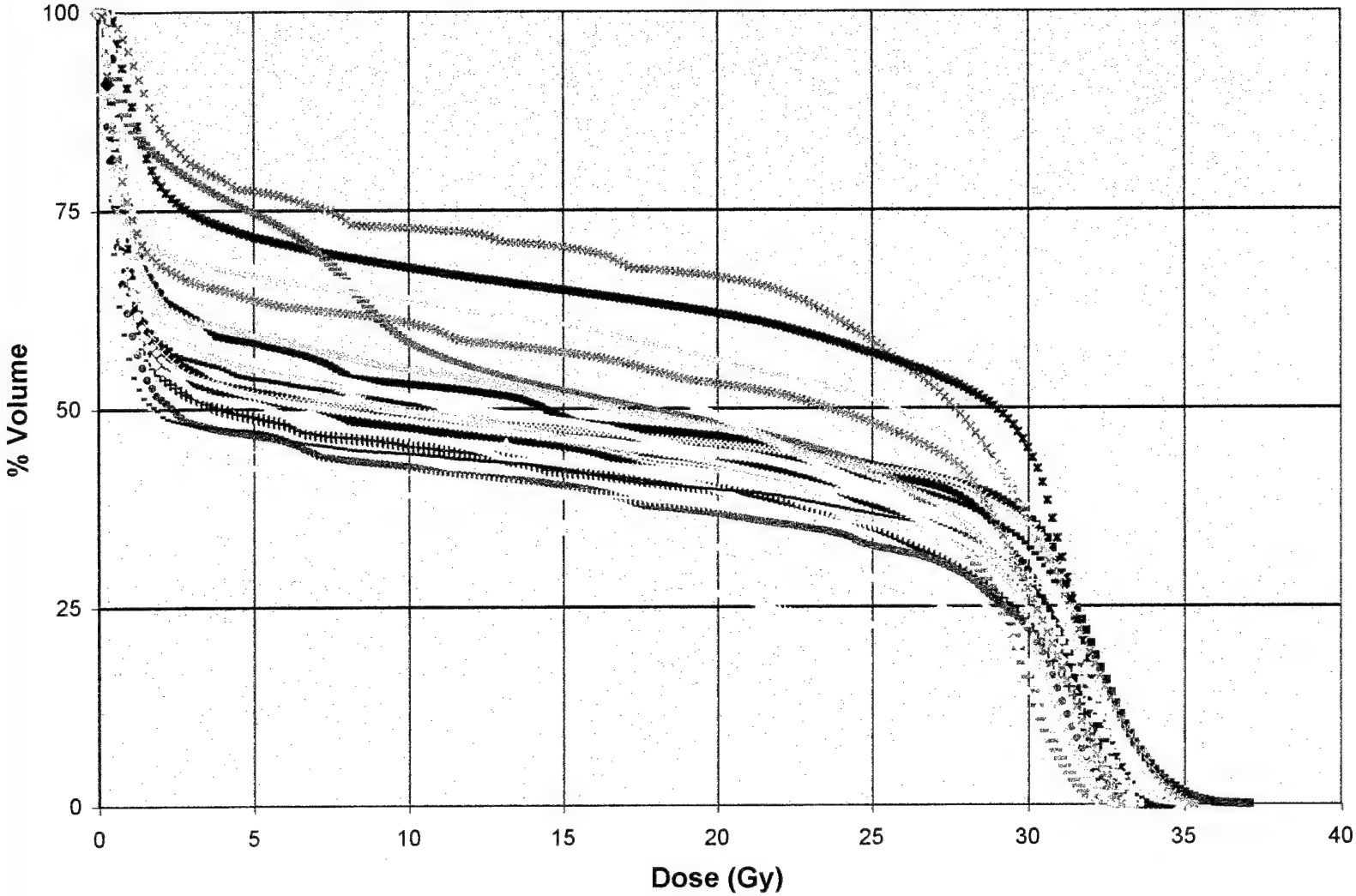
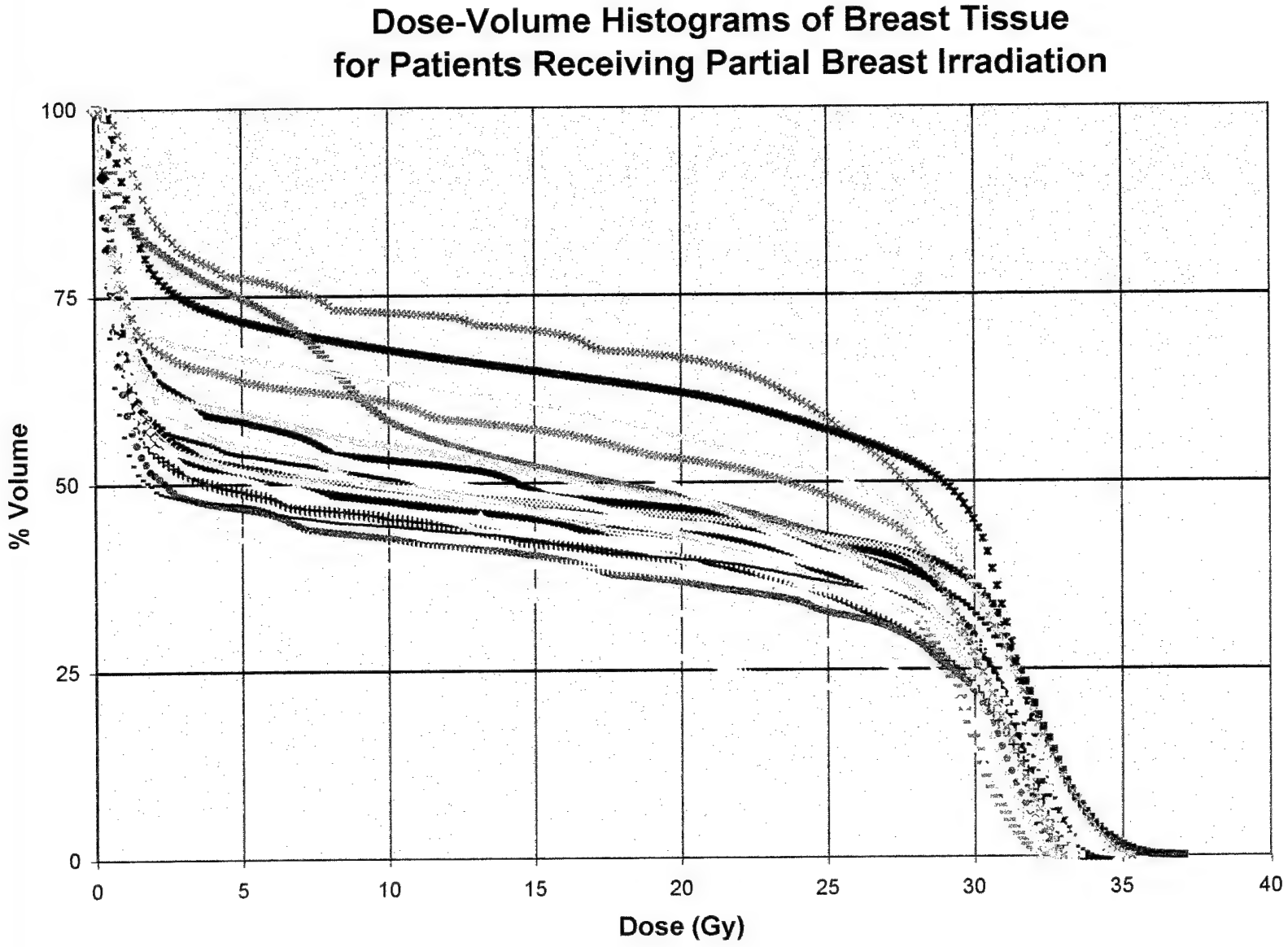
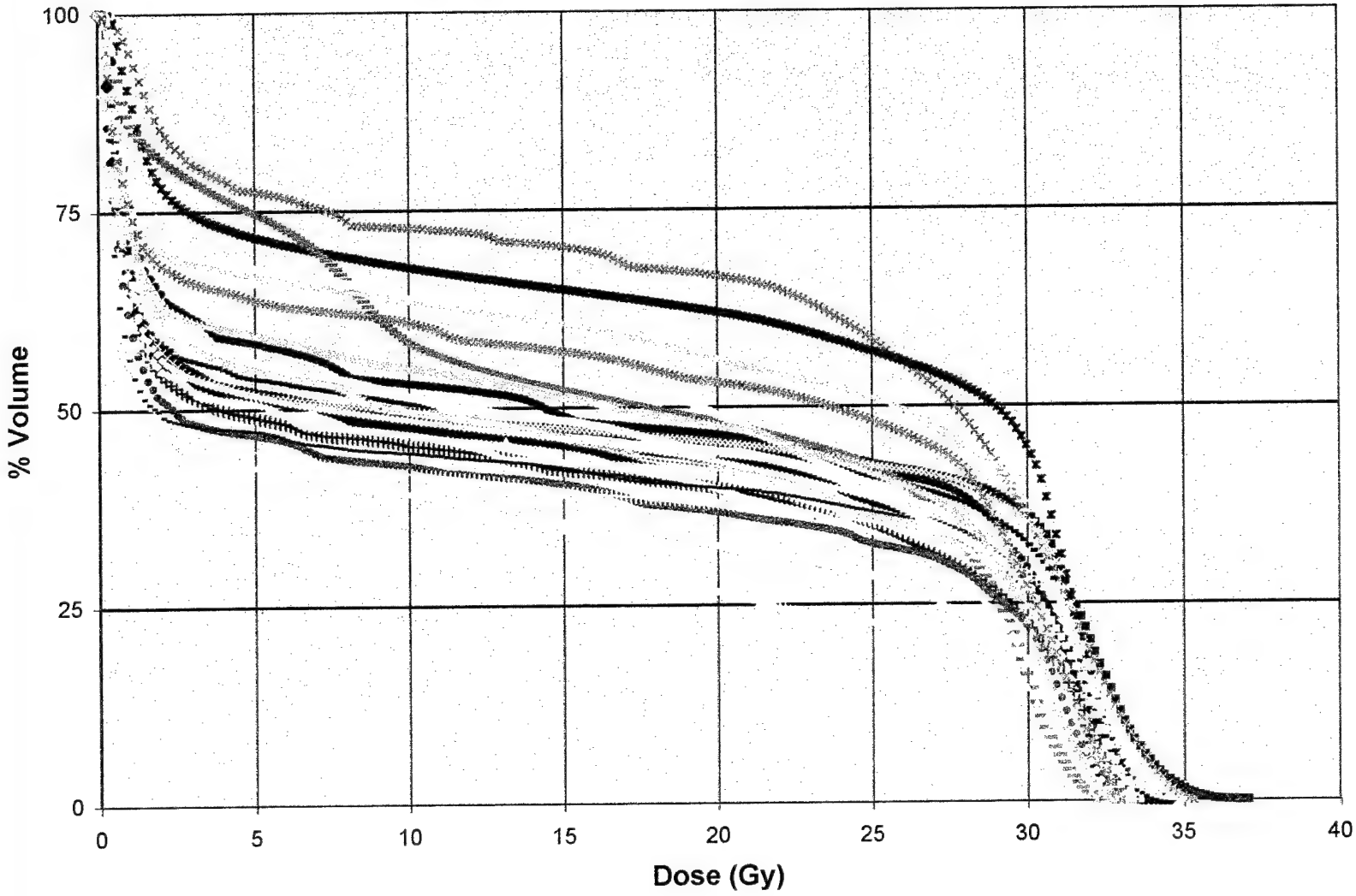


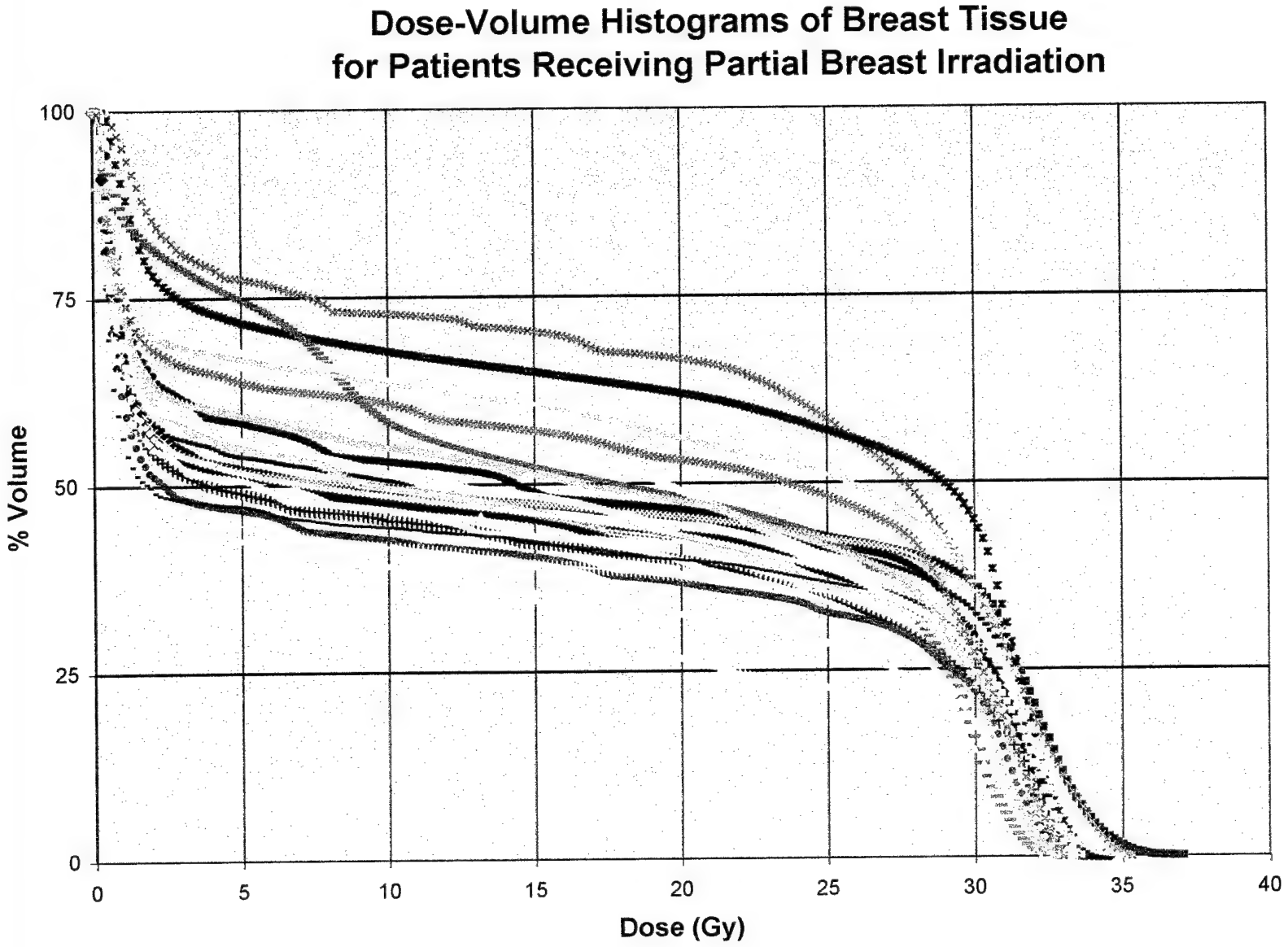
Dose-Volume Histograms of Breast Tissue for Patients Receiving Partial Breast Irradiation




Dose-Volume Histograms of Breast Tissue
for Patients Receiving Partial Breast Irradiation
100
75
50
25
0
% Volume
0
5
10
15
20
25
30
35
40
Dose (Gy)

Dose-Volume Histograms of Breast Tissue for Patients Receiving Partial Breast Irradiation




Dose-Volume Histograms of Breast Tissue
for Patients Receiving Partial Breast Irradiation
100
75
50
25
0
% Volume
0
5
10
15
20
25
30
35
40
Dose (Gy)

Silvia C. Formenti, MD
Barry Rosenstein, PhD
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T1 Stage Breast Cancer: Adjuvant Hypofractionated Conformal Radiation Therapy to Tumor Bed in Selected Postmenopausal Breast Cancer Patients—Pilot Feasibility Study[1]

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Breast neoplasms, 00.32
Breast neoplasms, therapeutic radiology, 00.1269
Computed tomography (CT), treatment planning, 00.1211

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Abbreviation:
BED = biologically effective dose

PURPOSE: To explore the feasibility of a short course of hypofractionated conformal radiation therapy to the tumor bed as part of a breast preservation protocol in postmenopausal patients with nonpalpable pT1N0 stage breast cancer.

MATERIALS AND METHODS: The tumor bed was imaged at computed tomography (CT) in the prone position on a dedicated table. The same table and position were used for treatment with a 4-MV linear accelerator. The planning target volume was the tumor bed plus a 1–2-cm margin defined at postmastectomy CT. A regimen of five fractions was tested in this pilot dose study. Cosmesis was assessed by patients and physicians before treatment and 36 months after treatment.

RESULTS: Ten consecutive patients who were eligible for the study were assigned to one of three dose-per-fraction regimens; nine were treatable with the proposed technique on the basis of CT findings. Patients received five fractions over 10 days (total dose range, 25–30 Gy): Three received 5.0 Gy per fraction; four, 5.5 Gy; and two, 6.0 Gy. At minimum follow-up of 36 months (range, 36–53 months), all patients were alive and disease free with good to excellent cosmesis.

CONCLUSION: Hypofractionated conformal breast radiation therapy is feasible. Further studies are warranted.

[1] From the Department of Radiation Oncology, New York University School of Medicine, 566 First Ave, New York, NY 10016 (S.C.F., B.S.R.), and the Departments of Surgery (K.A.S.) and Radiation Oncology (G.J.), Keck School of Medicine, Los Angeles, Calif. Received April 12, 2001; revision requested May 11; revision received June 29; accepted July 5. Supported by Breast Research Grant Pilot Projects, IB-95-3 from NCI Norris Cancer Center Breast Cancer Research Program grant R21CA66222, 1995; Stop Cancer Award, 1996; and California Breast Cancer Research Program BCRP 2CB-0224, 1997. **Address correspondence to** S.C.F.

Author contributions:
Guarantor of integrity of entire study, S.C.F.; study concepts and design, S.C.F., G.J.; literature research, S.C.F., B.R.; clinical studies, K.A.S., S.C.F., G.J.; data acquisition and analysis/interpretation, K.A.S., S.C.F., G.J.; statistical analysis, S.C.F., G.J.; manuscript preparation, S.C.F.; manuscript definition of intellectual content, S.C.F., G.J., B.R.; manuscript editing, S.C.F., G.J.; manuscript revision/review, all authors; manuscript final version approval, S.C.F.

The rate of breast cancer detection has accelerated due to the ability to use screening mammography to identify small nonpalpable breast lesions (1–4). As a result, a new patient population is emerging that is composed of postmenopausal women with nonpalpable tumors measuring less than 2 cm in diameter that are detected at routine mammography. The natural history of these tumors is not well known since data are scarce, and controversy exists regarding their correct management (4–6). For instance, the role of systemic chemotherapy remains controversial, but adjuvant treatment with tamoxifen is almost always indicated (7).

Is the standard regimen of 6 weeks of postoperative radiation therapy necessary in this patient population? Results of a few studies have suggested a lower risk of local recurrence with segmental mastectomy alone than what is expected from classical histopathologic assessments of multifocality and multicentricity (8–10). However, the recent disclosure of results from the National Surgical Adjuvant Breast Protocol B-21 demonstrate that tamoxifen treatment alone is insufficient to prevent local recurrence even in women with tumors measuring less than 2 cm (11). On the other hand, alarming data are also emerging documenting that a sizable proportion (36%) of older women undergoing breast preservation surgery do not undergo postoperative irradiation, probably because of the difficulty of adhering to the standard protocol of 6 weeks of radiation therapy (12).

Could a more convenient fractionation regimen substitute for the current radiation therapy protocol? The safety of using a hypofractionated irradiation schedule is supported

by the results of a prospective randomized trial with 230 patients published by Baillet et al (13). Patients in this study were randomly assigned to receive 45 Gy in 25 fractions over 33 days or 23 Gy in four fractions (two fractions at 5 Gy and two at 6.5 Gy) over 17 days (hypofractionation group). With a minimum follow-up of 4 years at the time of publication, no difference in local recurrence rate (7% vs 5%) was detected between the two arms of the study. Among the patients who underwent breast preservation, however, telangiectasia was more prevalent (14% vs 9%) and there was twice the incidence of breast fibrosis (18% vs 9%) in those randomly assigned to the hypofractionation arm.

Building on the French experience (13), we decided to pilot test the role of hypofractionated radiation therapy to a target treatment volume smaller than the entire breast, with the intent of reducing the risk of fibrosis and poor cosmesis, which are more likely to occur when the entire breast is treated with large radiation fractions. We based our rationale for treating only part of the breast on the pattern of in-breast recurrence when irradiation is omitted. Four prospective randomized trials (14–17) that tested the hypothesis of avoiding postoperative irradiation in early breast cancer have generated information about the geographic profile of recurrence after partial mastectomy alone: The large majority of local recurrences occur at the original tumor bed. Moreover, evidence is available to suggest that the risk of recurrence outside the original tumor bed in the ipsilateral breast appears be similar to that of new tumors in the contralateral breast (16,18,19) (Table 1).

These findings suggest that adjuvant radiation therapy to a volume inclusive of the tumor with sufficient margins might be adequate to markedly reduce the risk of local recurrence in women with T1 stage breast cancer. The issue is quite relevant, since a reduction in the target volume of irradiation permits the consideration of more convenient fractionation regimens and allows us to challenge the existing paradigm of radiation treatment. Initially, we developed a radiosurgery-like approach to investigate, as part of an institutional review board–approved study, the biologic effect of a large single fraction given preoperatively to T1 stage breast cancers measuring less than 1 cm. The technical and physical components of such an approach were previously reported (20). After the first three patients, however, we elected to interrupt the study because of findings of multifocality at surgery in two patients.

TABLE 1
Breast Cancer Incidence after Breast Preservation Surgery: Ipsilateral Breast Outside of Tumor Bed versus Contralateral Breast

Study	Follow-up	Incidence (%)	
		Ipsilateral Breast	Contralateral Breast
Fisher et al (18)	39 mo	1.3	2
Veronesi et al (16)	39 mo	1.5	1.5
Dalberg et al (19)	13 y	1.8	4

TABLE 2
BEDs and Response to Irradiation

Response	α/β	Standard Regimen	Hypofractionation Regimen		
		30 Fractions of 1.8 Gy	Five Fractions of 5.0 Gy	Five Fractions of 5.5 Gy	Five Fractions of 6.0 Gy
Erythema	8	66	41	46	53
Desquamation	11	62	36	41	46
Telangiectasia	4	78	56	65	75
Fibrosis	2	103	88	103	120
Tumor	2	103	88	103	120
Tumor	4	78	56	65	75

Note.—Data are in grays.

It became evident to us that a larger volume of breast needed to be included if partial breast irradiation were to be tested postoperatively: Consequently, the original protocol developed into a pilot study of hypofractionated radiation therapy to partial breast tissue. We used a previously described (20) dedicated treatment table that allows both prone computed tomographic (CT) imaging of the breast and conformal treatment with a 4-MV linear accelerator (Linac 4; Varian Medical Systems, Palo Alto, Calif) in the same position. Thus, the purpose of this study was to explore the feasibility of a short course of hypofractionated conformal radiation therapy to the tumor bed as part of a breast preservation protocol in postmenopausal patients with nonpalpable T1 stage breast cancers detected at mammography who were to receive tamoxifen.

We limited the size of this pilot study to 10 patients and elected to observe them for a minimum of 36 months before accruing new patients to this study.

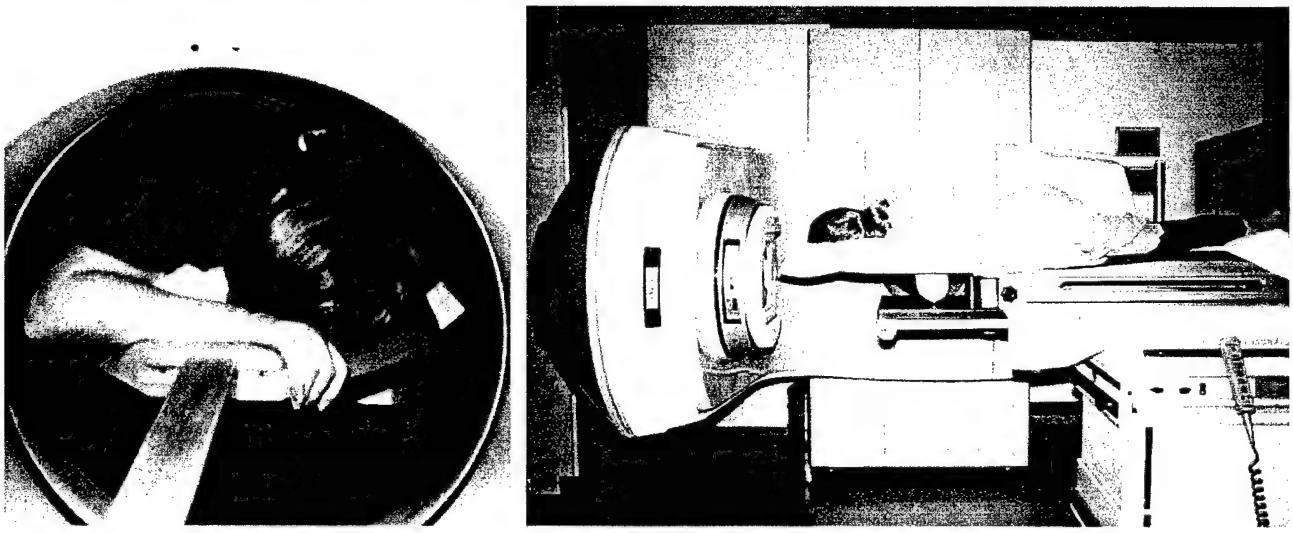
MATERIALS AND METHODS

Calculation of Biologically Effective Dose

The biologically effective dose (BED) for each treatment condition was calculated by using the following equation (21): $\text{BED} = (n \times d)(1 + d/\alpha/\beta)$, where n is the number of fractions, d is the dose per fraction, and α/β is a value for the particular tissue and response. It was assumed for all calculations that full repair takes place during the 24-hour or longer interval between fractions.

Table 2 lists the standard and hypofractionation treatment BEDs for tumor control, in addition to the early responses, erythema and desquamation, and late responses, telangiectasia and fibrosis. The α/β values used for these computations were reported in previous studies (23–28). The normal tissue complication BEDs were generally lower for the hypofractionation schedules compared with those for standard treatment, suggesting a diminished risk for radiation-induced effects. The only instance yielding an increased BED was for skin fibrosis at the highest dose. However, it must be kept in mind that the treatment was conformal to the tumor bed, and, therefore, a smaller volume of skin was irradiated, compared with irradiation with the standard treatment. This may have somewhat lessened both the severity and the probability of fibrosis compared with the probability after whole-breast irradiation.

As for tumor control, the BEDs calculated with the α/β value set at 4 Gy, as



a. b.

Figure 1. (a) A patient undergoes CT in a diagnostic scanner while lying prone in the treatment position on the dedicated treatment table. (b) The same patient is ready to receive treatment in the imaging position.

suggested in experiments involving irradiation of human breast cancer cell lines (23,28,29), were comparable to the standard treatment for the highest dose schedule but were lower for the other two treatment plans. However, on the basis of the results of a previous randomized study of a hypofractionation schedule (13), an α/β value of 2 Gy may be more accurate for breast carcinoma. The tumor BEDs were therefore recalculated by using an α/β value of 2 Gy, which yielded similar BEDs for the hypofractionation and standard schedules. Hence, the probabilities for tumor control associated with the hypofractionation schedules were comparable to that for standard treatment.

On the basis of the BEDs listed in Table 2, the patients were randomly assigned to one of three sets of dose-per-fraction schedules, 5.0, 5.5, or 6.0 Gy daily five times over a 10-day period, since the BEDs for both tumor and normal tissue effects associated with these treatments were within the same range as those calculated for a standard treatment.

Patient Eligibility

Patients eligible for entry into this pilot feasibility study were postmenopausal women who had undergone segmental mastectomy for newly diagnosed nonpalpable T1 stage invasive breast cancer. Other requirements were pT1 stage tumor, estrogen receptor positive, with lack of an extensive intraductal component and negative surgical margins of at least 2 mm. In all patients, tamoxifen was prescribed as a systemic adjuvant treatment. Patients were initially offered a standard regimen of 6 weeks of radiation therapy. Breast size and shape were not limiting criteria for eligibility to this study. All patients provided signed informed consent.

Patients and tumor characteristics were recorded by one of the authors (S.C.F.) and included age, date of initial pathologic diagnosis of breast cancer, tumor size and nodal status at pathologic examination, number of radiation therapy fractions, dose per fraction, and total radiation dose received. Local or distant recurrence was recorded by two of the authors (S.C.F., K.A.S.).

From the described radiobiologic considerations, a dose per fraction of 5–6 Gy in five fractions was predicted to be the closest equivalent to the conventional regimen of 30 fractions of 2 Gy each. We elected to investigate 5.0, 5.5, and 6.0 Gy per fraction. The three tested doses per fraction were randomly assigned (from a list generated in the clinical research office of the cancer center) to avoid some of the more common investigator-generated biases (ie, entry of "safer" patients at lower dose levels or of higher risk patients at higher dose levels). Patients who refused to undergo 6 weeks of irradiation were eligible, and all patients were required to provide signed informed consent to participate in the study.

Patient Positioning and Treatment Setup

The patient was placed in the prone position on a specially designed treatment table (Fig 1). The table has an aperture with variable diameter, which allows the breast to hang down. The specifications of the design have been previously described (20). Since the last 63 cm of the table does not have any support from underneath the main board where the patient lies, the hanging breast can be irradiated from a large spatial angular interval. The treatment couch rotation range is approximately 220°, while the gantry rotation range is 180° when the couch is not rotated and 90° otherwise (20). The end of the table bends less than 5 mm below the horizontal plane when the patient is on the table. Bending at the breast level is visually undetectable.

Once imaging and treatment planning were completed, the patient was set up daily by referring to markings on the skin and the treatment table after placement of BB markers, as previously described (20). When radiopaque markers (clips) were not left in the breast, more external markers were used to facilitate accurate reproduction of the treatment position. Lateral and oblique port films were obtained to verify the treatment position. The verification was accomplished by comparing the port films with digitally reconstructed radiographs produced by the treatment planning software (20). For each patient treated daily, setup accuracy

was verified with a set of orthogonal port films before each radiation fraction was delivered. In addition, at least two fields were ported every time.

Target Definition Treatment Planning

The table is built of wood and does not contain metallic parts in the region of interest, therefore it can be used for CT imaging without the result of any metal artifact on the images. CT images obtained in the treatment position were downloaded to our treatment-planning software. The physician outlined the target volume on the basis of information obtained from the surgery report, mammography results, or other available examination results. If radiopaque surgical clips were present, the process of marking the boundaries of the surgery to outline the target volume was greatly simplified. We defined the planning target volume as the tumor cavity identified at CT planning plus a 2-cm margin. The prescription dose was defined as the minimum dose that encompassed 95% of the planning target volume. The maximum dose was not to exceed the prescription dose by more than 10%.

The open-ended table enabled the application of multiple arcs with different table rotations. However, parts of the arcs inevitably would result in irradiation of nonbreast tissue (eg, lung); therefore, in most cases, the treatment field selection was limited to five to seven horizontal fixed beams in the coronal plane (Fig 2). The field sizes were adjusted to the projection of the planning target volume.

Assessment of Cosmetic Result

During the first visit to the radiation oncology department, each patient was asked to assess the cosmetic result achieved after breast surgery by using the cosmesis score reported by Gray et al (22). The subjective analysis of cosmetic outcome was grouped as follows: 9–10, excellent; 7–8, good; 5–6, fair; and 4 or less, poor. The indexes evaluated were symmetry, breast edema, skin thickening, breast tissue fibrosis, retraction, telangectasia, and dimpling. The same evaluation was performed at 36-month follow-up. At these follow-up evaluations, the doctor and the patient both scored the cosmetic result with the same four score categories.

RESULTS

From January 1997 to June 1998, 10 consecutive eligible patients were entered into the study. Three patients received 5.0 Gy per fraction; four received 5.5 Gy per fraction; and three were assigned to receive 6.0 Gy per fraction, only two of whom were treated. One of the latter three patients in the 6.0-Gy per fraction group was determined not to be treatable with the present technique because of original tumor location. All remaining patients were treated daily five times over a 10-day period. In all nine patients treated, the dose prescription requirements were achieved. The average number of treatment fields used was five (range, three to eight; median, five).

Table 3 describes the characteristics of the accrued patients. The median age was 65 years (range, 58–85 years). In two patients, no axillary node dissection was performed: in one (patient 6) because of tumor size, and in the other (patient 4) because of the patient's refusal. Six patients underwent level I and II axillary dissection and had no nodal metastases; in two patients, axillary dissection was avoided because of negative sentinel node biopsy findings.

Figure 3 describes the findings of a typical patient (patient 9) whose lesion was suitable for treatment with the proposed technique. At digital radiographic reconstruction, clips in the patient's breast were used to identify a volume that cleared the projection of the treatment table both on transverse (Fig 3a) and sagittal (Fig 3b) projections. BB markers were also displayed to ensure reproducibility of the clinical setup during treatment after initial CT imaging. In Figure 4, transverse (Fig 4a) and sagittal (Fig 4b) displays of planning target volume and isodose distributions in patient 9 are shown.

Among the 10 patients accrued and randomly assigned to the three radiation

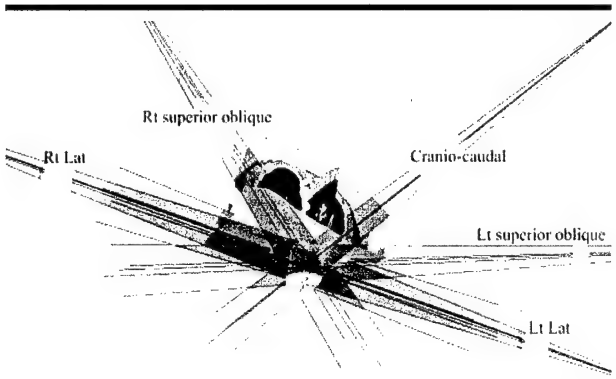
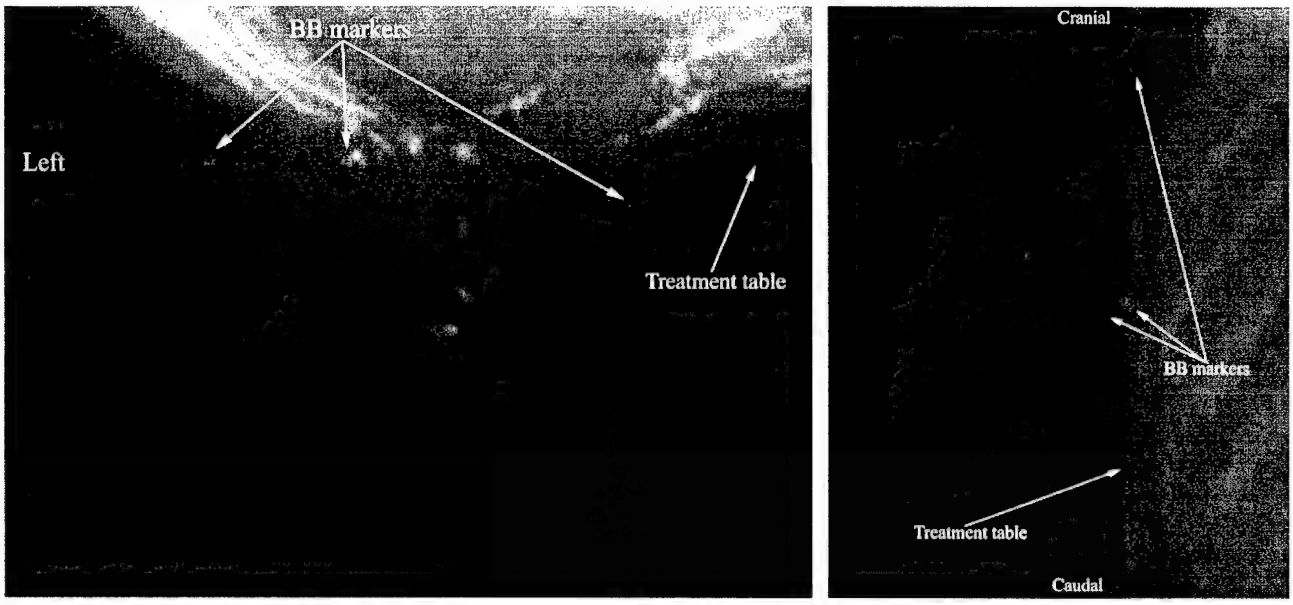


Figure 2. Three-dimensional graphic reconstruction of five "beam-eye views" used in the treatment of a patient. All beams exit below the dedicated treatment table. The reconstruction was limited to the hanging breast containing the target volume; the rest of the patient and the dedicated table are not displayed. *Lat* = lateral, *Lt* = left, *Rt* = right.

TABLE 3
Patient Characteristics and Treatment Specifications

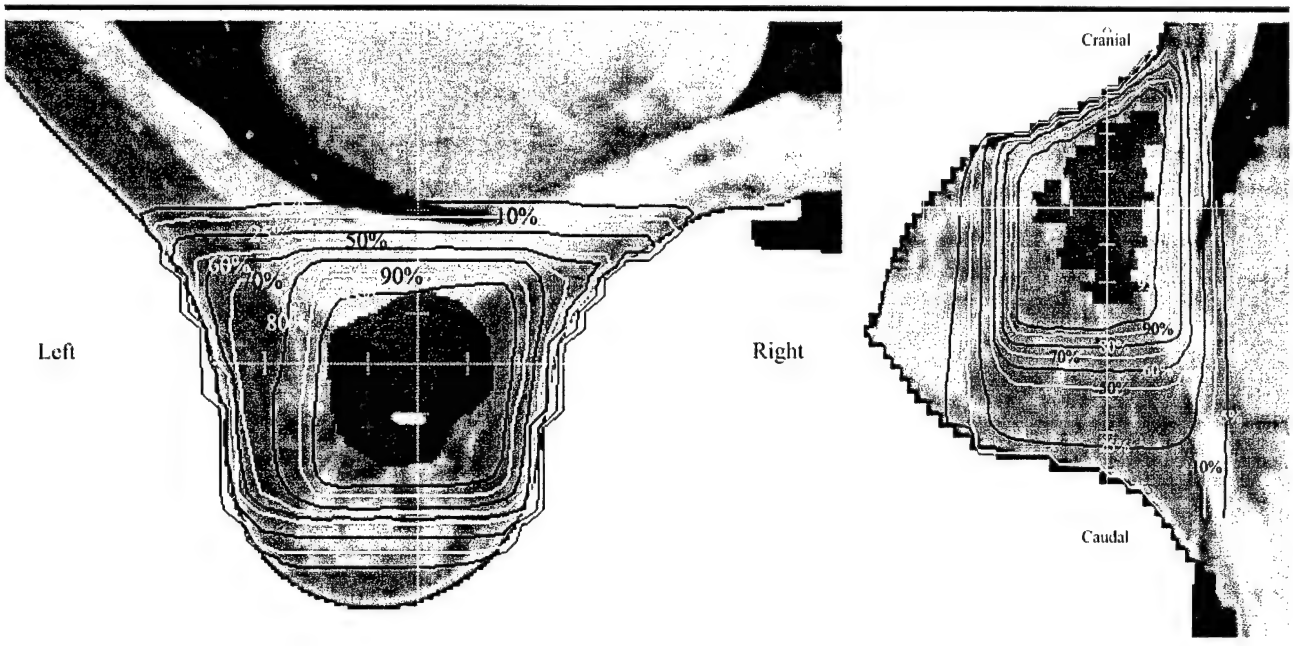
Patient No./ Age (y)	Tumor Size (cm)	Lymph Nodes*	Dose per Fraction/ Total Dose (Gy)
1/76	0.7 × 0.5 × 0.5	0/10	5.5/27.5
2/69	1.0 × 0.8 × 0.5	0/13	5.0/25.0
3/65	1.5 × 1.3 × 1.0	0/23	6.0/30.0
4/74	1.6 × 1.5 × 1.3	NA	5.5/27.5
5/66	1.5 × 1.2	0/23	6.0/30.0
6/78	0.5 × 0.5	NA	5.0/25.0
7/85	1.4 × 1.0 × 1.0	0/15	5.5/27.5
8/60	1.0 × 1.0	0/7	5.0/25.0
9/60	1.2 × 1.2	0/sentinel	5.5/27.5
10/58	0.7 × 0.6 × 0.5	0/sentinel	Not applicable

Note.—All patients were treated with five fractions, except patient 10, who was not treated owing to original tumor location.
* Data are number of metastatic nodes/number of resected nodes at axillary dissection. NA = not available.



a. b.

Figure 3. Example in patient 9, who had a lesion suitable for treatment with the proposed technique. (a) Transverse and (b) sagittal digital radiographic reconstructions show clips in the patient's breast that were used to identify a volume that clears the projection of the treatment table.



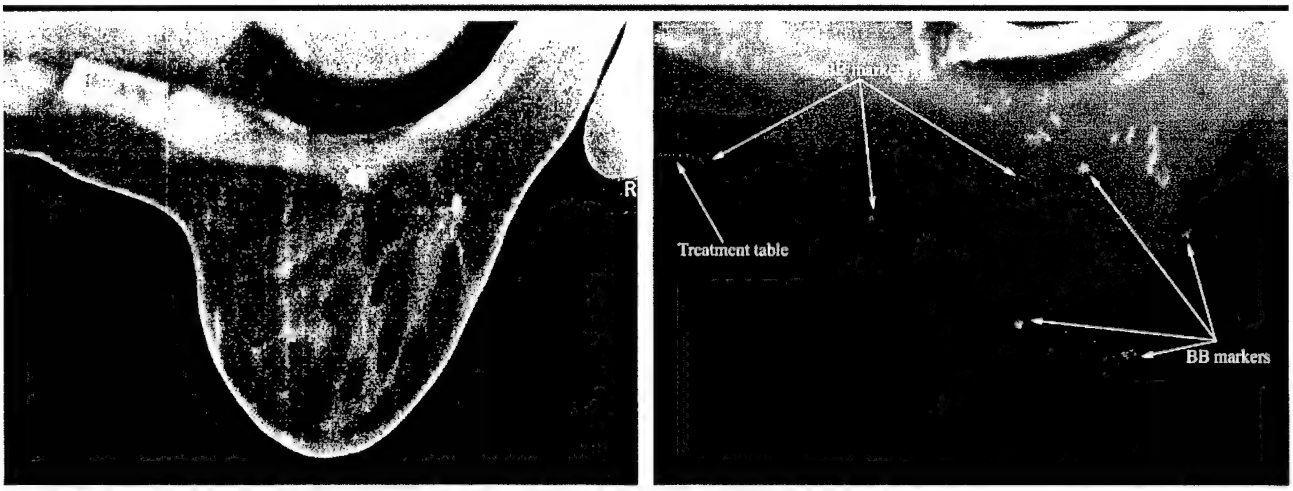
a. b.

Figure 4. Patient 9. (a) Transverse and (b) sagittal displays of planning target volume and isodose distributions.

fractions studied, one patient (patient 10), assigned to the 6.0-Gy level was determined to be technically nontreatable with the proposed technique because of the location of the original tumor within the tail of Spence. Because of the proximity to the chest wall of the volume enclosed by the surgical clips (Fig 5a), which did not clear the treatment table (Fig 5b), patient 10 could not be treated with this technique.

For each patient treated, a good correspondence (<5-mm difference) between the port film set and the reconstructed digital radiograph for that specific field was achieved. The average time on the table was 25 minutes (range, 18–47 minutes); on several occasions, some patients complained of discomfort encountered while remaining still in the prone position. No patient, however, requested an interruption in treatment.

Minimum follow-up for the 10 patients was 36 months (range, 36–53 months).



a. b.

Figure 5. (a) Transverse CT image in patient 10, who was found after randomization not to be treatable with the proposed technique because of the proximity to the chest wall of the volume enclosed by surgical clips. (b) Transverse digital radiographic reconstruction shows that the volume delineated by the markers did not clear the treatment table.

TABLE 4
Follow-up and Treatment Outcome

Patient No.	Last Follow-up Date*	Outcome†	Postoperative Cosmesis Assessment‡	Postirradiation Cosmesis Assessment at Last Follow-up	
				Patient	Doctor
1	5/4/2001	NED at 41 mo	Good	Good	Good
2	6/1/2000	NED at 53 mo	Excellent	Excellent	Excellent
3	6/5/2001	NED at 41 mo	Excellent	Excellent	Good
4	5/6/2001	NED at 40 mo	Excellent	Excellent	Good
5	6/5/2001	NED at 46 mo	Excellent	Excellent	Excellent
6	1/4/2001	NED at 45 mo	Good	Good	Good
7	7/2/2000	NED at 38 mo	Excellent	Excellent	Excellent
8	3/6/2001	NED at 45 mo	Excellent	Excellent	Excellent
9	6/1/2001	NED at 36 mo	Good	Good	Excellent
10	5/3/2001	NED at 39 mo	Good	Not applicable§	Not applicable§

* Date is presented as month/day/year.
† NED = no evidence of disease.
‡ Measured by patient just before start of radiation therapy.
§ Patient could not be treated with the studied technique.

With regard to cosmetic results, none of the nine treated patients has developed radiation changes with regard to symmetry, breast edema, skin thickening, breast tissue fibrosis, retraction, telangectasia, and dimpling at the time this report was written. All patients have maintained the same self-assessment of the cosmetic result after treatment when compared with the pretreatment assessment. Similarly, the assessment of cosmetic result performed by the doctors (S.C.F. and K.A.S.) ranged from good to excellent for all patients treated.

At the time this report was written, none of the patients have shown clinical or radiologic local recurrence of breast cancer. All patients are alive without evidence of clinical or radiologic regional or distant metastases (Table 4).

DISCUSSION

The treatment approach pilot tested in this study introduces two variations when compared with the current standard regimen after segmental mastectomy: hypofractionation and partial breast radiation therapy.

Historically, breast cancer was effectively treated with large radiation fractions (30–33). Both acute and delayed complications were already well described in 1949 by Baclesse (33), who discovered that for each fractionation regimen, the therapeutic ratio was largely dependent on field size. Baclesse advocated the use of a "sufficient number of contiguous small fields in rotation" as the future of breast cancer radiation therapy. More recently, the prospective randomized trial of Baillet et al (13) has provided evidence that, with a limited follow-up of 4 years, hypofractionation treatment is as effective as 45 Gy in 25 fractions. An obvious criticism of this study is the fact that the control arm was itself underdosed, since it is likely that a regimen of 45 Gy in 25 fractions may be inadequate, especially in view of the fact that 61% of the patients in the study had a T2 stage tumor and 17% had a T3–T4 stage tumor. Nevertheless, the relatively low rate of local

recurrence (considering the original tumor size distribution) and its comparability in the two arms is encouraging. As expected, fibrosis and telangectasia were more frequent in the hypofractionation arm (13).

To reduce the risk of poor cosmesis and fibrosis, could a regimen of hypofractionated irradiation be safely limited to a volume smaller than the whole breast? Traditionally, the concept of limiting radiation treatment to part of the breast has been discouraged by the findings from pathologic studies (10,34,35) with mastectomy specimens in which frequent multifocality and multicentricity associated with even small breast cancers were reported.

However, this concept must be revisited in view of the evidence generated by several prospective randomized trials (14–17) in which local recurrences in breast cancer patients who had not undergone irradiation were demonstrated to occur almost exclusively at the original tumor bed. It is conceivable that even in small breast cancers, the process of wound repair that follows surgical manipulation might favor tumor bed recurrence (36,37), as demonstrated by the high local recurrence rate encountered in the original study (38) from the joint center that omitted radiation therapy in women with T1 stage fully excised breast cancers. Consequently, postsegmental mastectomy radiation therapy to the tumor bed appears to remain a necessity in all invasive breast cancers, independent of tumor size and excision margins.

Several groups have explored in phase I and II studies the use of brachytherapy to treat less than the entire breast tissue (39–42). An external-beam approach is more likely to *(a)* be more acceptable to the patient, *(b)* be more widely reproducible, and *(c)* generate better dose homogeneity and cosmetic results than brachytherapy (43,44). Evidence is also emerging that preoperative blood levels of tumor growth factor–β1, or TGF-β1, could help identify patients more likely to develop radiation-induced fibrosis (45).

Our results suggest that in nine of 10 eligible patients, hypofractionated conformal radiation therapy of the tumor bed was feasible and well tolerated. It appears that a tumor location very close to the chest wall may represent an exclusion criterion. While a conformal approach was possible because most patients in this pilot study had clips that could be used to determine the location and extent of the tumor bed, in the absence of clips it may be necessary to treat larger volumes, comparable to a quadrant of breast tissue, to ensure coverage of the tumor bed.

The choice of the three hypofractionation schedules used in this study was based on the calculated BEDs listed in Table 2. As for normal tissue responses, with the exception of fibrosis at the highest dose used, none of the treatment protocols yielded BEDs greater than the standard schedule. Therefore, an increased incidence of normal tissue responses would not have been expected. Even for the one dose in which the hypofractionation BED was high, it must be kept in mind that only a portion of the breast was irradiated, thereby likely decreasing the probability of a fibrotic reaction, as compared with the likelihood after whole breast radiation therapy.

With respect to tumor control, the classic dilemma typically encountered when a hypofractionation protocol is substituted for a standard treatment plan is either a reduced probability of tumor control or an increased risk for late complications. This is due to the observation that fractionation generally results in greater sparing of late-responding tissues relative to tumors. This finding is reflected in the relatively large α/β values derived for tumors and the small α/β values for late responses. However, in contrast to this generalization, evidence exists that breast cancer cells display a relatively low α/β value. This comes from in vitro studies (23,24,28) in which α/β values determined for breast cancer cell lines were generally about 4 Gy. However, an even lower α/β value of 2 Gy can be calculated by using the results of the existing prospective randomized trial (13) in which a standard treatment of 25 1.8-Gy fractions resulted in roughly the same level of tumor recurrence as a hypofractionation protocol of two 4.5-Gy plus two 6.5-Gy fractions. Therefore, it can be assumed that the BEDs for the two treatments were about the same, and on this basis an α/β value of 2 Gy was computed.

It should also be noted that the hypofractionation schedules represent accelerated treatments because the total treatment time was 10 days, compared with a standard protocol in which the total radiation dose is delivered over 39 days. Hence, the actual BED of the standard protocol is somewhat lower than the values reported in Table 2 and can be determined by using the equation $[(n \times d)(1 + d/\alpha/\beta)] - [\ln 2(T - T_k)/\alpha(T_{pot})]$, where n is the number of fractions, d is the dose per fraction, T is the total length of treatment, T_k is the time at which accelerated repopulation begins, and T_{pot} is the potential doubling time of the tumor (21, 46). In contrast, accelerated repopulation would not have been expected during the 10-day hypofractionation treatments, and, thus, the BED values should not be adjusted. However, this correction was not attempted since there have been no specifically established values for α and T_k for breast cancers. In addition, the median T_{pot} value for breast cancers has been reported to be roughly 13 days (47,48), and use of this relatively high value would produce only small decreases in BEDs. It is also true that the BEDs for early responses would be diminished if proliferation during treatment is taken into account. However, since the early-response BEDs for the hypofractionation schedules were so much lower than the standard treatment BEDs (Table 2), it is unlikely that inclusion of a cellular proliferation correction would change the order of these BEDs.

Finally, the population of women targeted in this pilot study could particularly benefit from a radiation therapy technique that excludes the heart, because recent epidemiologic evidence suggests that, in postmenopausal women, a large part of the survival benefit derived from postoperative irradiation is abolished by the increased risk of vascular disease after radiation therapy (49).

Since the completion of 36 months of follow-up for all the patients treated in this pilot study, we have started a prospective phase II study. The aims of the this study are *(a)* to explore the efficacy of this approach when compared with historical local control rates achieved with standard postoperative radiation therapy, *(b)* to prospectively assess the pretreatment role of circulating tumor growth factor–β1 as a marker for posttreatment fibrosis, and *(c)* to pilot test the use of ultrasonography for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator radiation beams in the absence of surgical clips. The trial uses the two-stage "mini-max" design of Simon (50) and will enroll at most 99 patients (α = .05; power = .80). This phase II study will generate the necessary data for a future phase III study to establish whether hypofractionated partial breast radiation therapy is as effective as the conventional 6-week protocol in this patient population.

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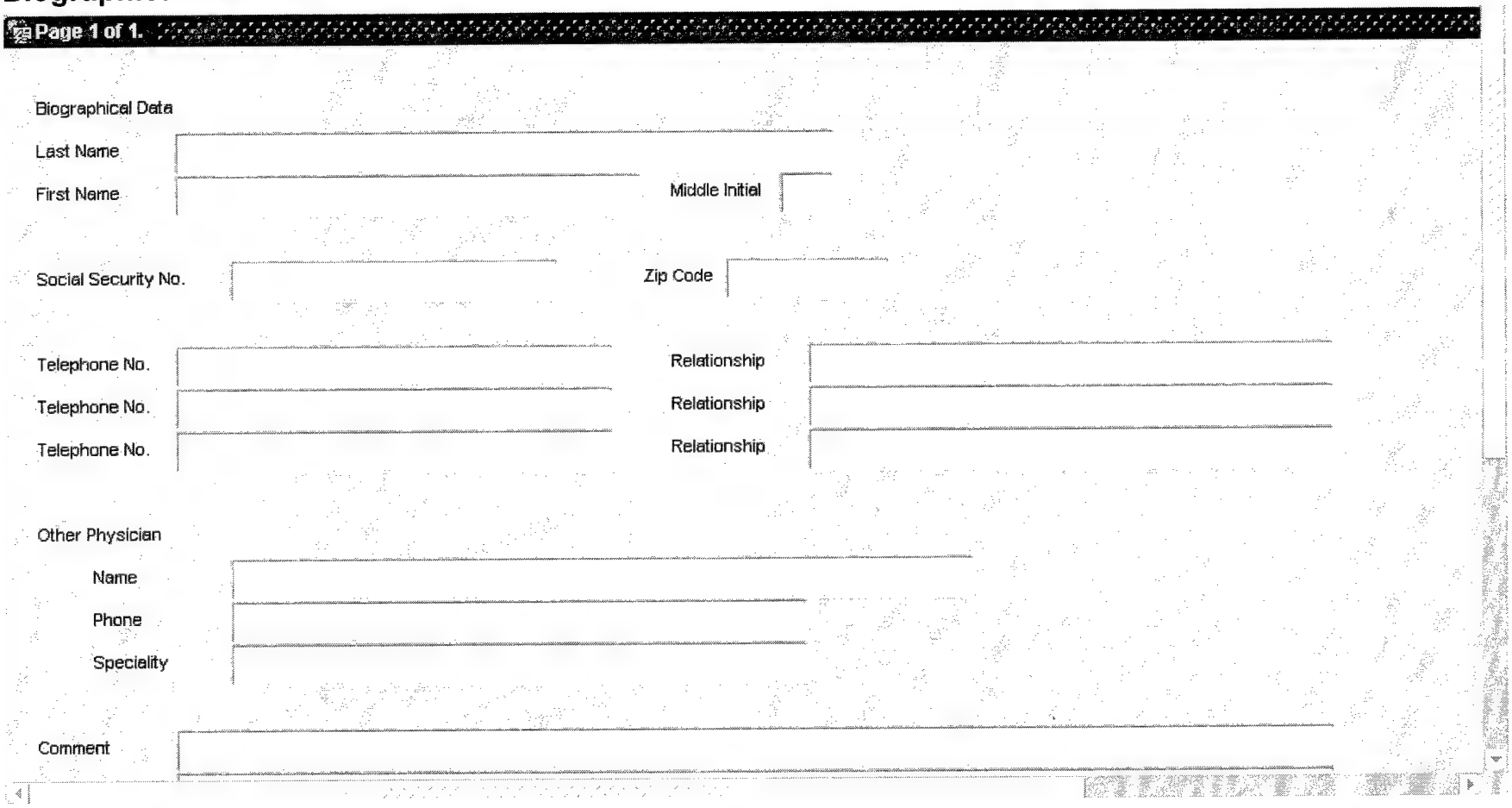
NYU CANCER INSTITUTE

STUDY: NYU 00-23

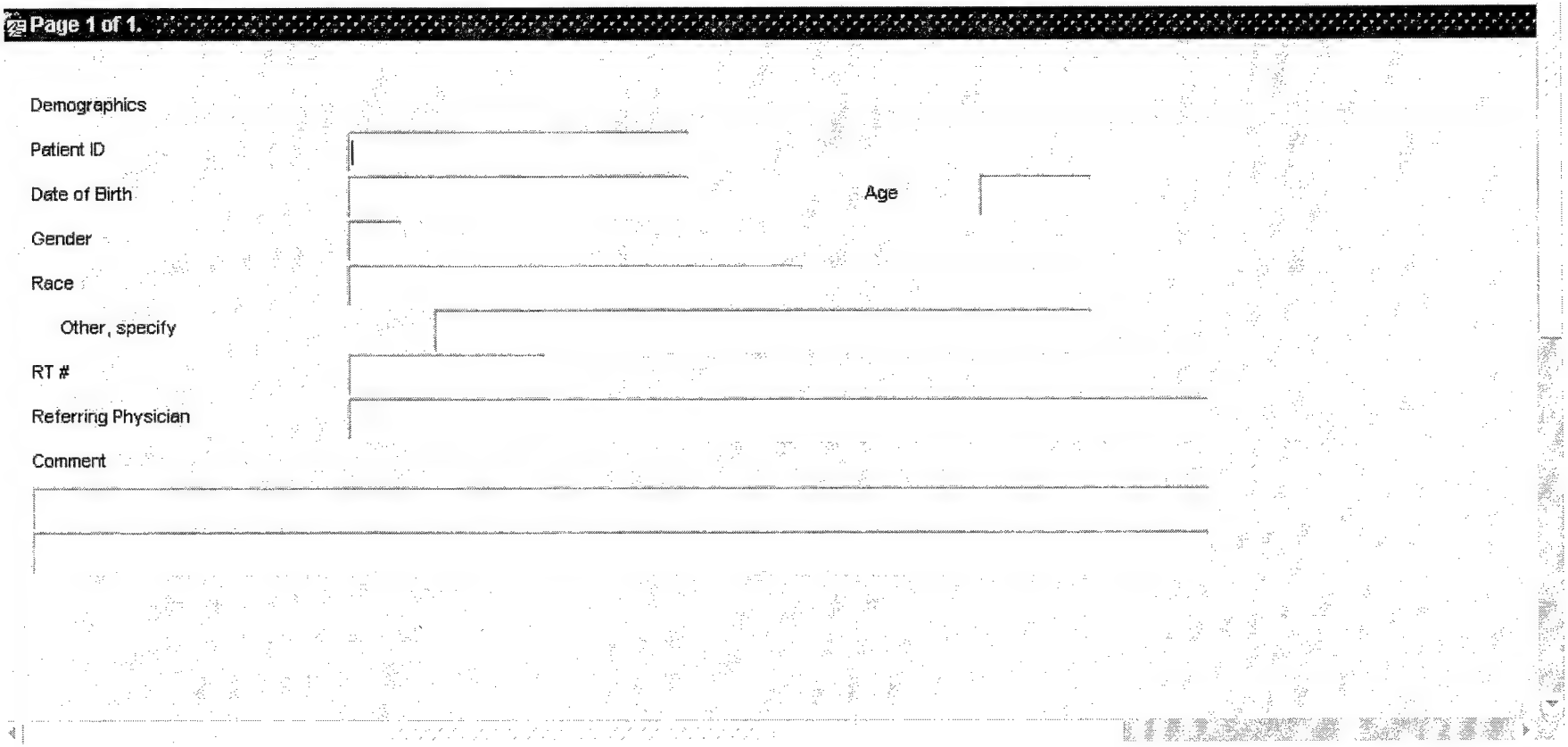
ORACLE CLINICAL DATA CAPTURE

Screen Shots Only

Biographical Data DCM



Demography DCM



Disease Diagnosis DCM

Page 1 of 1.

Breast Cancer Diagnosis

Side

T:

N:

M:

Mammography Date

Excision Date

Path Diagnosis Date

Tumor Characteristics

ER:

PR:

Her2 Test:

Her2-neu by IHC:

Her2-neu by FISH:

Prior Hormone Usage ---- HRT Use

Tamoxifen Use

Raloxifene Use

Note: Use 'Current' for use at time of mammogram or breast cancer diagnosis.

Comment

Prior Treatment DCM

Page 1 of 1, Repeat 1 of 13.

Prior CancerTreatment

	Code	Any Therapy ?	If therapy, enter date of last dose
CHEMOTHERAPY SINGLE	23518		
CHEMOTHERAPY MULTIPLE	23514		
CHEMOTHERAPY (NOS)	900102		
HORMONAL	23557		
SURGERY	4058		
IMMUNOTHERAPY	900104		
EXTENSIVE RADIATION	900106		
LIMITED RADIATION	900108		
RADIATION (NOS)	900110		
BONE MARROW TRANSPLANT	3487		
GENE THERAPY	900114		
PRIOR THERAPY (NOS)	900112		
NON-CYTOTOXIC CHEMOTHERAPY	900116		

Comment

Medical History DCM

Medical History

Visit Date

Body System

Body System	Normal?	Inactive conditions	Active conditions
CARDIOVASCULAR			
RESPIRATORY			
GI			
RENAL/ UROLOGY			
INFECTIOUS DIS			
NEUROLOGY			
RHEUM/ AUTOIM			
ENDO/ METAB			
REPROD/ BREAST			
PSYCHOLOGIC			
HEMATOLOGIC			
DERMATOLOGIC			
OPHTHALMOLOGIC			
ENT			

Comment

Screening DCM (Eligibility)

Page 1 of 1.

Date of Informed Consent

Waiver Information:

Eligibility Criteria - Yes/No		Y/N	Date	Granted By
1. PT1 BREAST CANCER WITH NEGATIVE MARGINS		NO		
2. ORIGINAL TUMOR NON-PALPABLE		NO		
3. pN0 / sentinal node negative / clinically N0 if tumor		NO		
4. Post menopausal woman (2 yrs since LMP / FSH i		NO		
5. PREVIOUSLY UNTREATED IPSILATERAL BREAST		NO		
6. PATIENT DECLINES 6 WEEKS CONVENTIONAL RA		NO		
7. Patient is receiving Tamoxifen		NO		
8. Proportion of DCIS in tumor is incompatible with El		NO		
9. NO SUSPICIOUS MICROCALCIFICATION AT POST		NO		

Confirming Data:

Exact tumor size (mm)

Age at menopause

nodes sampled

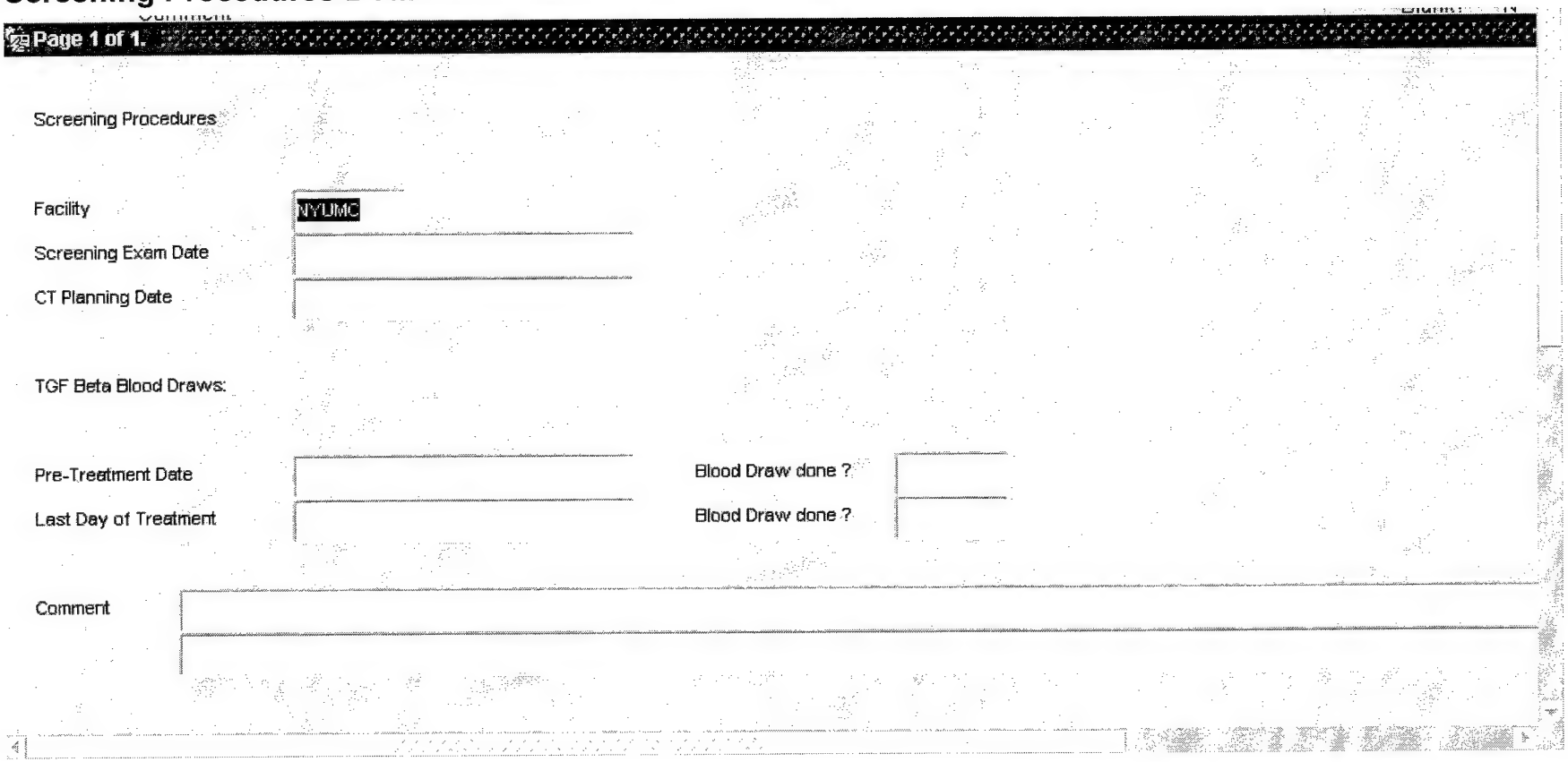
% DCIS

Date started Tamoxifen

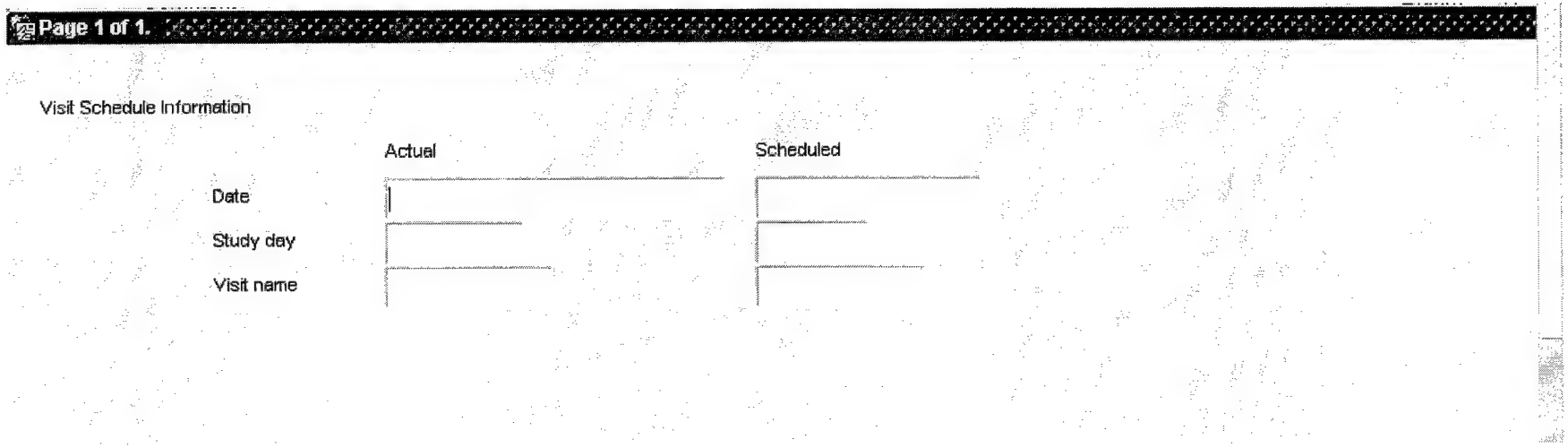
Comment

Patient Protocol Eligible

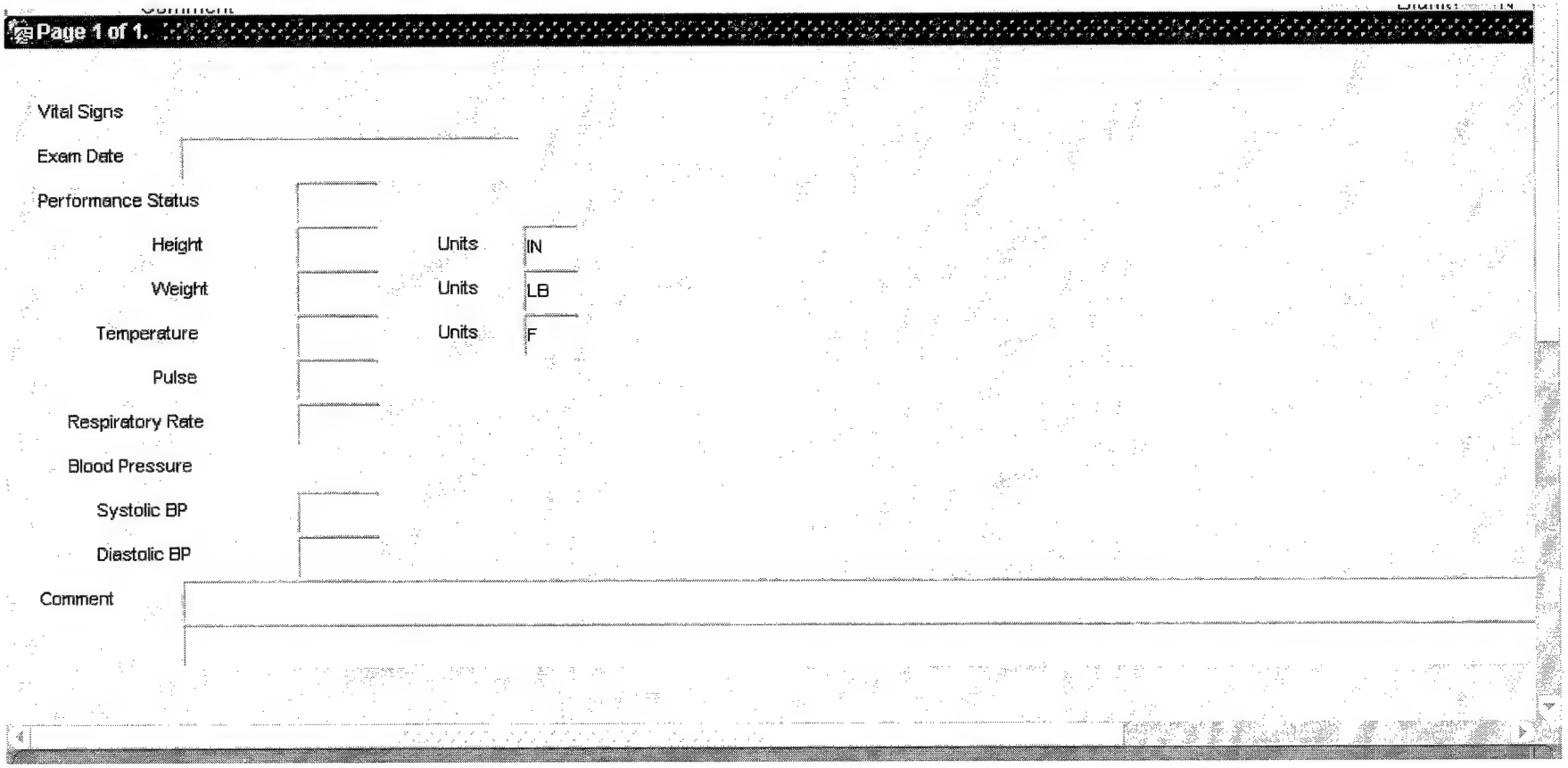
Screening Procedures DCM



Visit Information DCM



Vitals DCM


Page 1 of 1.
Vital Signs
Exam Date
Performance Status
Height
Units
IN
Weight
Units
LB
Temperature
Units
F
Pulse
Respiratory Rate
Blood Pressure
Systolic BP
Diastolic BP
Comment

Physical Exam DCM – baseline

Exam Date

Body System	Normal?	If abnormal, please comment:
HEAD / NECK		
RESPIRATORY		
CARDIOVASCULAR		
ABDOMEN		
PELVIS/GENITALIA		
BREASTS		
SKIN/ LYMPH NODES		
NEUROLOGIC		
EXTREMITIES		

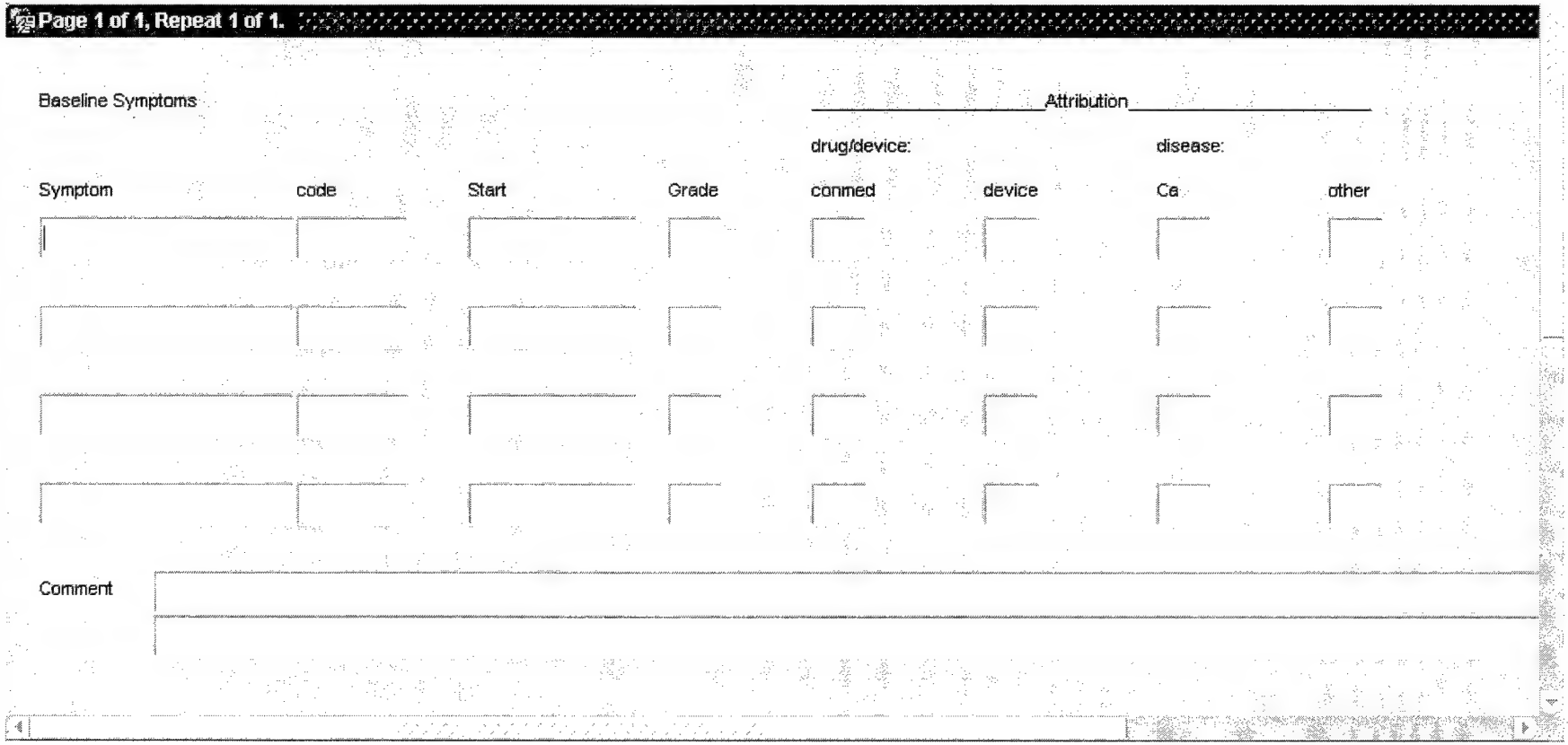
Comment

Physical Exam DCM – later visits

Page 1 of 1.

Exam Date		Change from	Any recurrence since last visit?	
Body System	Normal?	Baseline?	If changed from baseline, please comment.	
HEAD / NECK				
RESPIRATORY				
CARDIOVASCULAR				
ABDOMEN				
PELVIS/GENITALIA				
BREASTS				
LYMPH NODES				
SKIN				
NEUROLOGIC				
EXTREMITIES				
Comment				

Baseline Symptoms DCM



Clinical Labs DCM

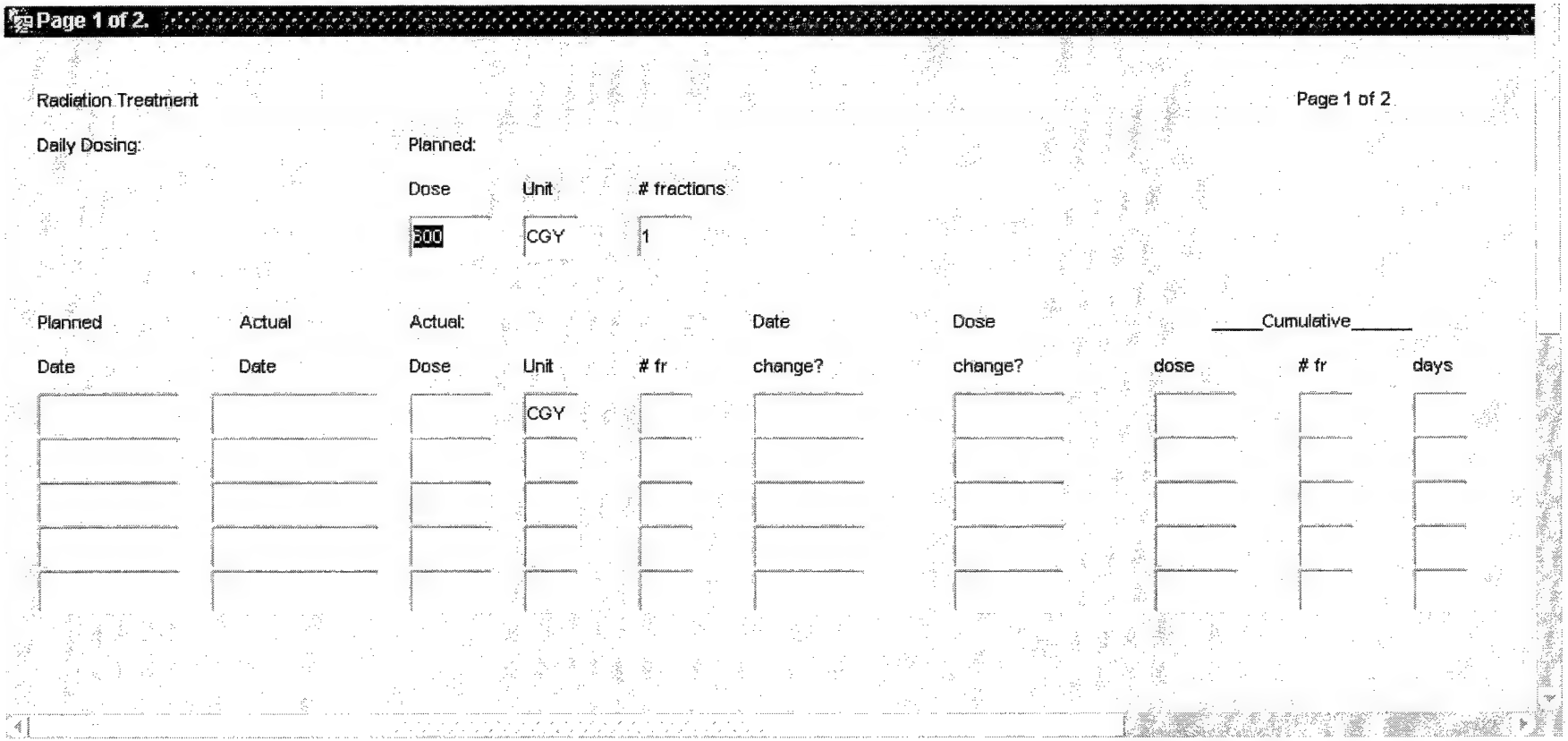
1	of	1	DCM	LAB	Subset	LABS	Layout	1	Blank?
					LAB	NYUMC$DEFAULT			

Clinical Laboratory Test Results

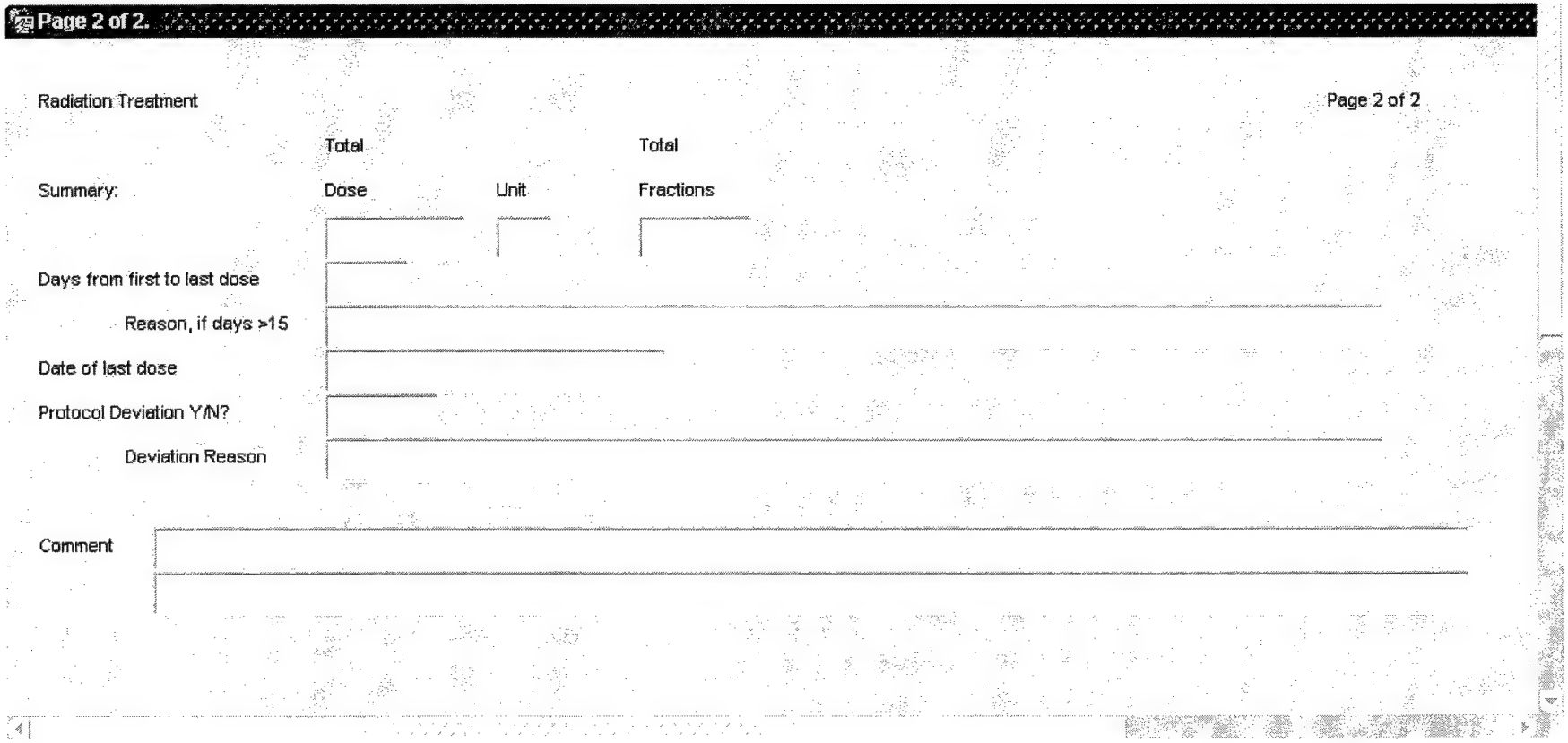
CBC		Chemistry		Liver Profile	
HGB		sodium		Total Protein	
Platelets		potassium		Albumin	
ANC		chloride		Alk Phos	
or		creatinine		Total bilirubin	
Neut %		BUN		ggt	
WBC		calcium		sgot/ast	
Derived ANC				sgpt/alt	

Comment

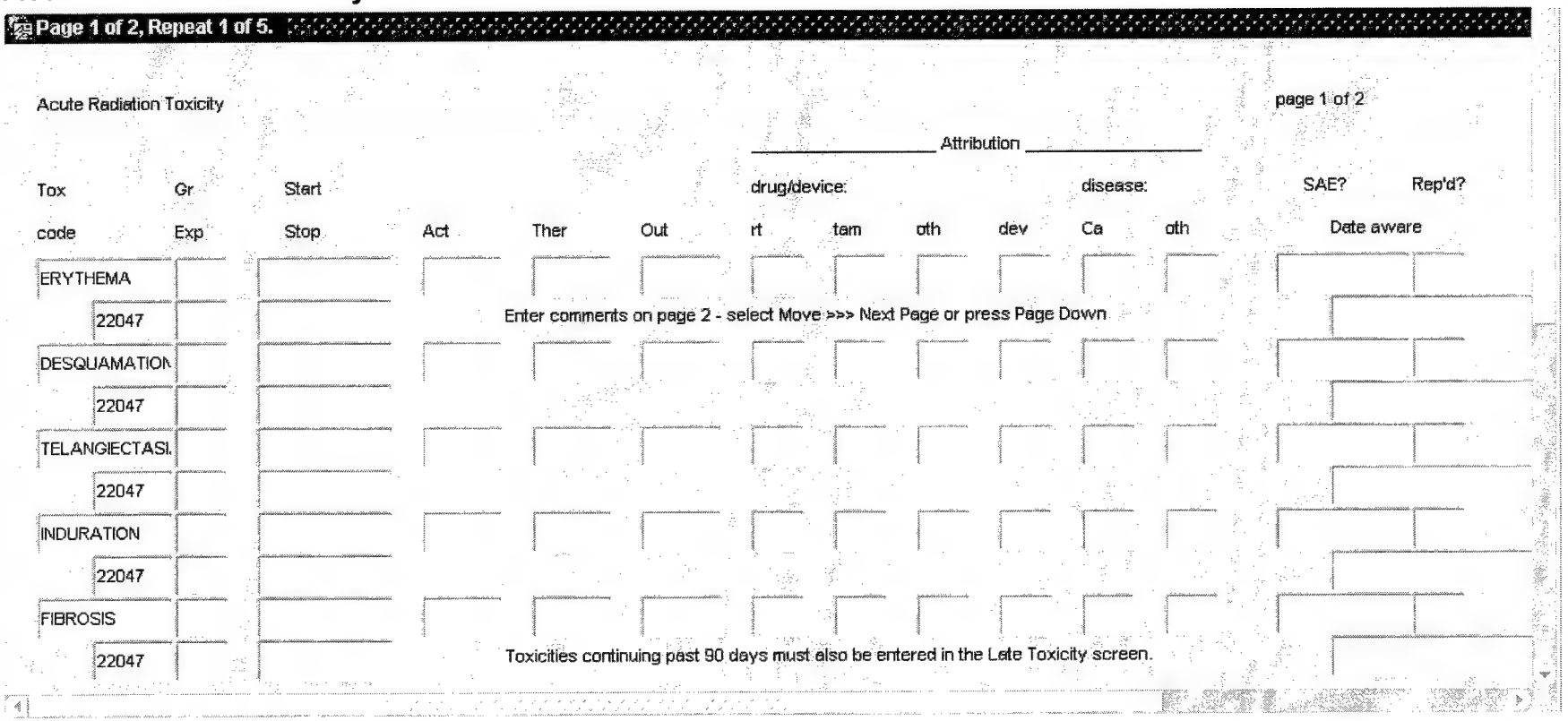
Radiation Treatment DCM



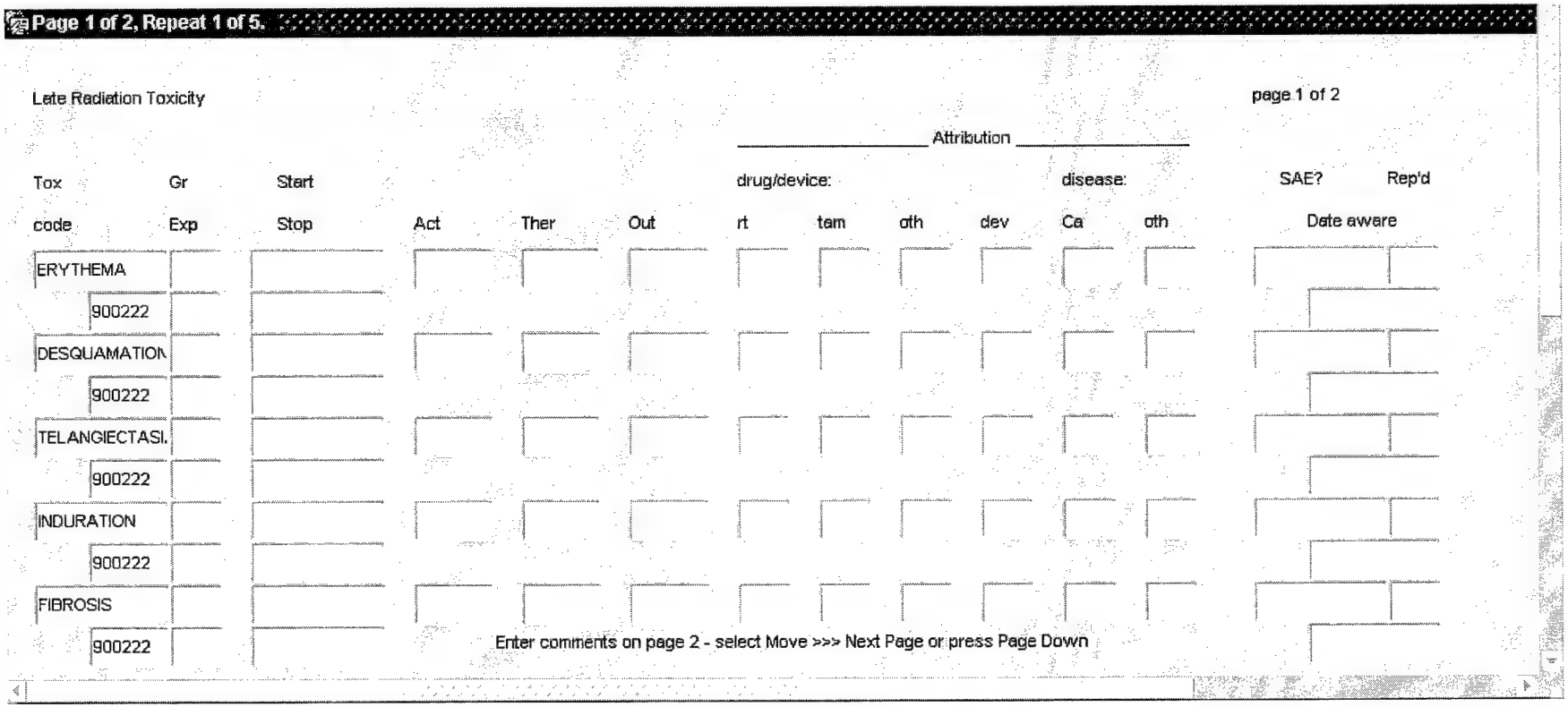
Radiation Treatment DCM – page 2.



Acute Radiation Toxicity DCM



Late Radiation Toxicity DCM



Adverse Events DCM

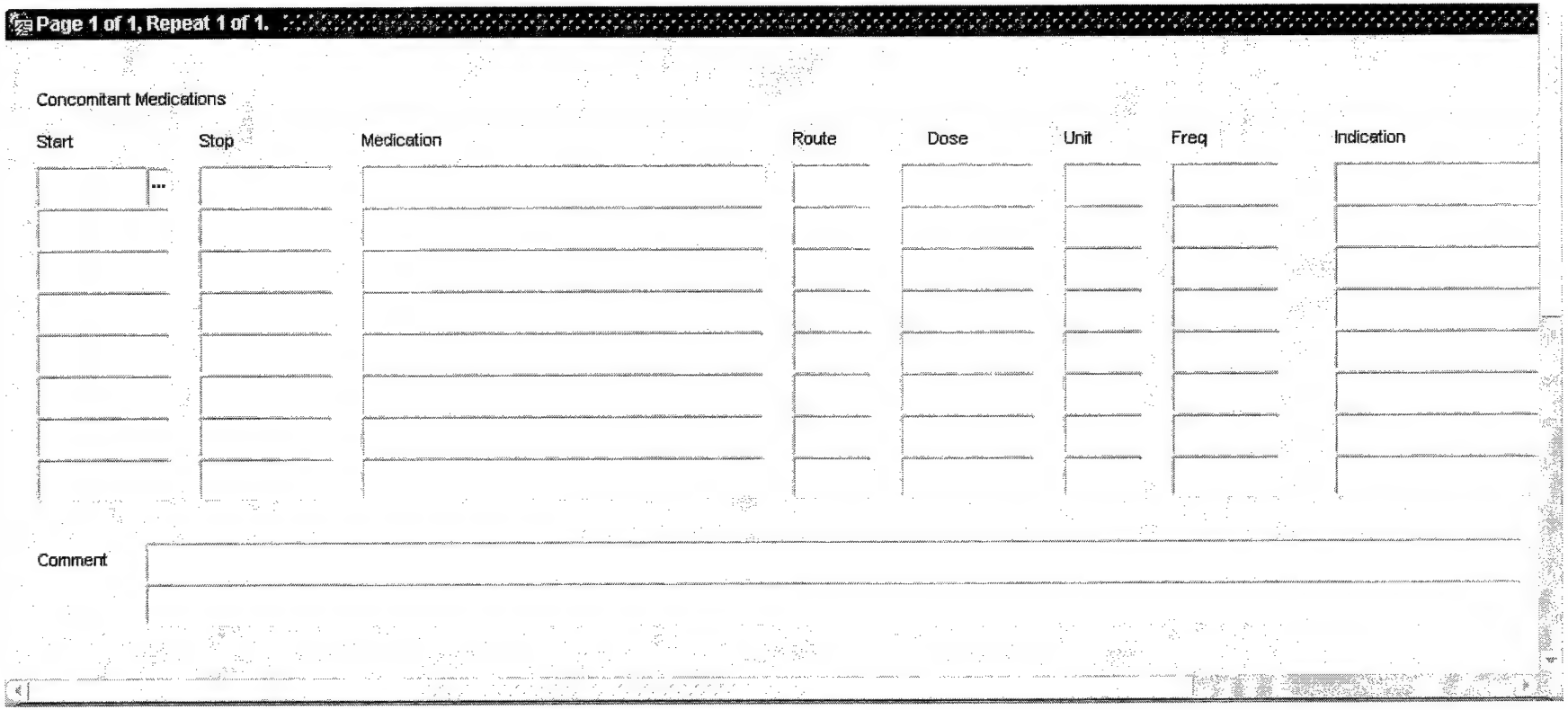
Page 1 of 1, Repeat 1 of 1.

Adverse Events, except RT skin toxicities

AE code	Start Stop	Gr Exp	Act	Ther	Out	Attribution: drug/device: rt	tam	oth	dev	disease: Ca	oth	SAE?	Rep'd? Date aware
FATIGUE 1423													

Comment

Concomitant Medication DCM



Tamoxifen (Study Drug) Administration DCM

Page 1 of 1, Repeat 1 of 12.

Study Drug Administration

Study Drug	Start Dt	Time Start	Stop Dt	Time Stop	Lot No.	Act. Dose	Act. dose units	Schedule	Route
TAMOXIFEN									
TAMOXIFEN									
TAMOXIFEN									
TAMOXIFEN									

Comment

Disease Recurrence DCM

Page 1 of 1.

Breast Cancer Recurrence

Any recurrence?

Type of Recurrence

Date of Recurrence

Time to Recurrence

Comment

Last Follow-up DCM (Off-Study)

Off Study

Off Study Date

Reason

If reason is death, complete the following:

Date of Death

Cause of death

Describe further details

Died with disease?

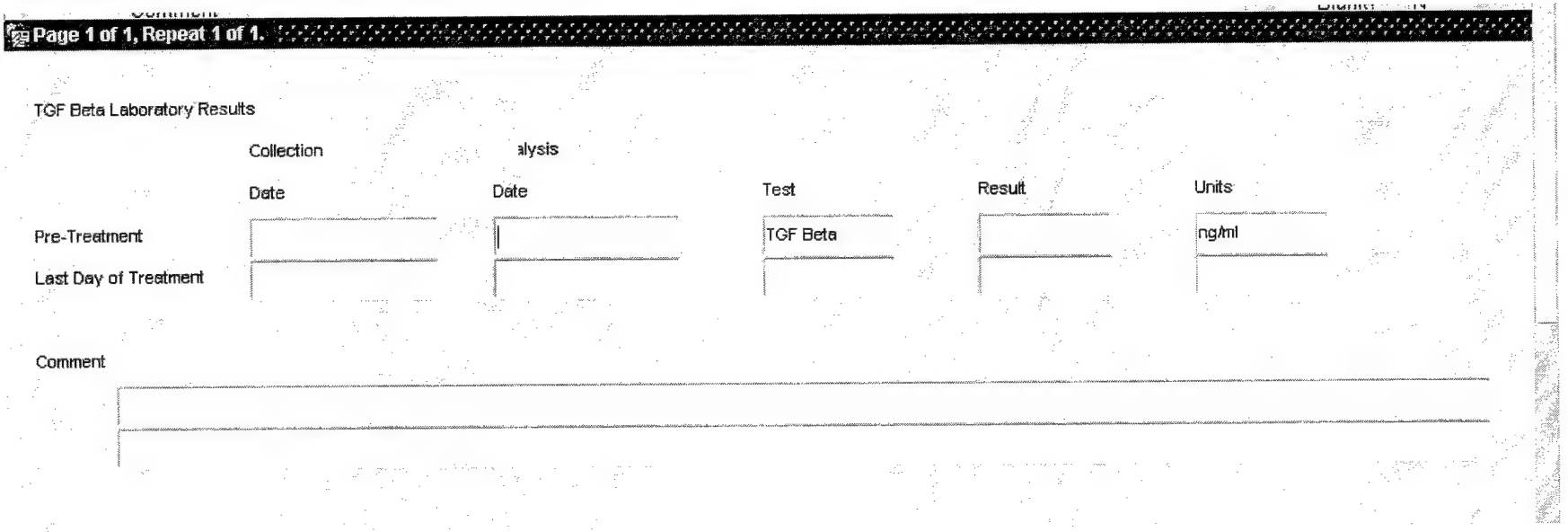
Total Follow Up Time (days)

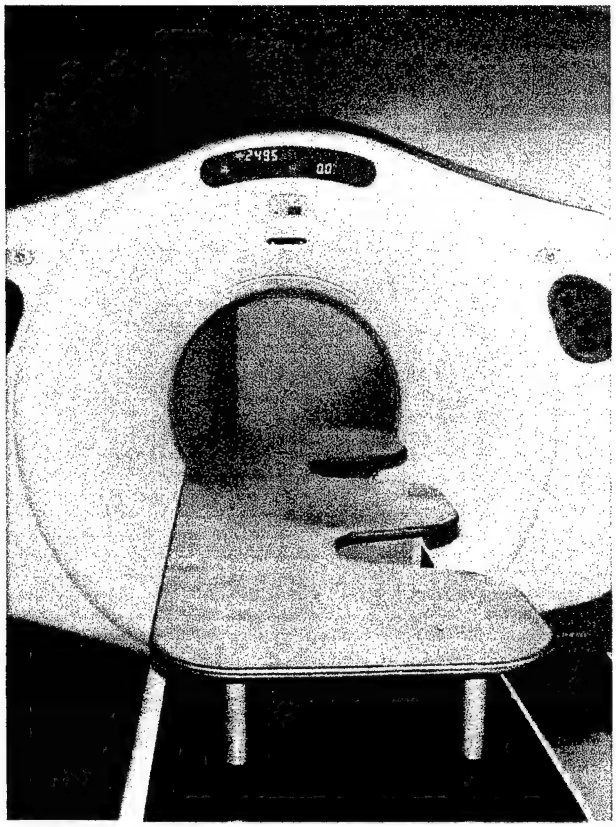
Evaluable for Recurrence?

Evaluable for TGF-Beta?

Comment

TGF Beta Lab DCM

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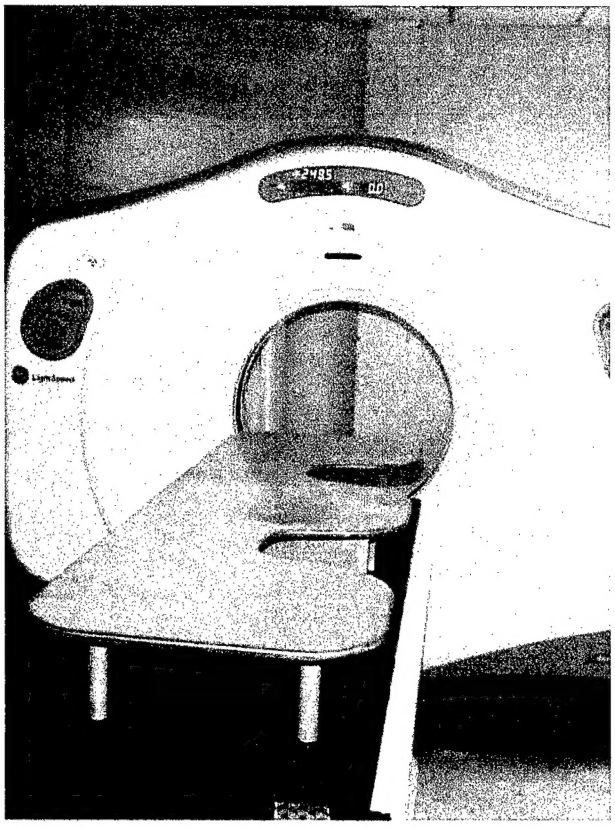
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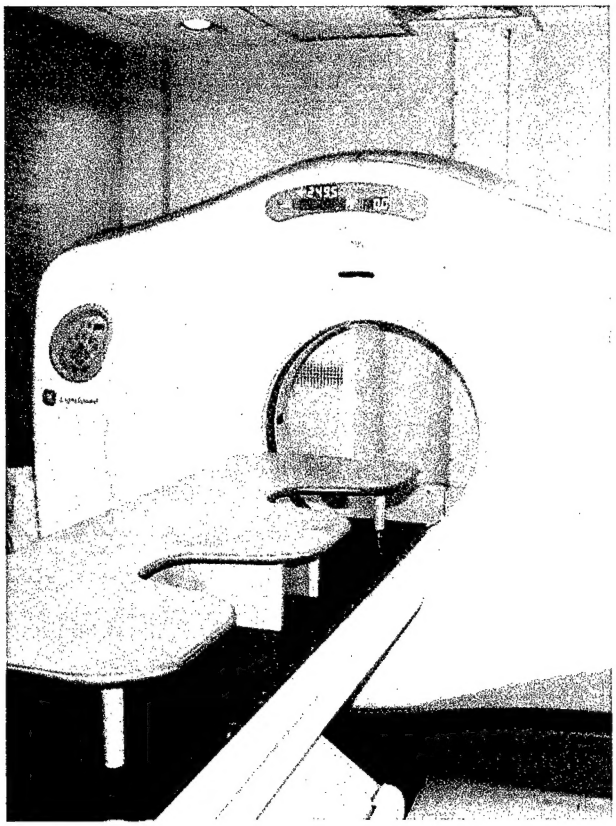

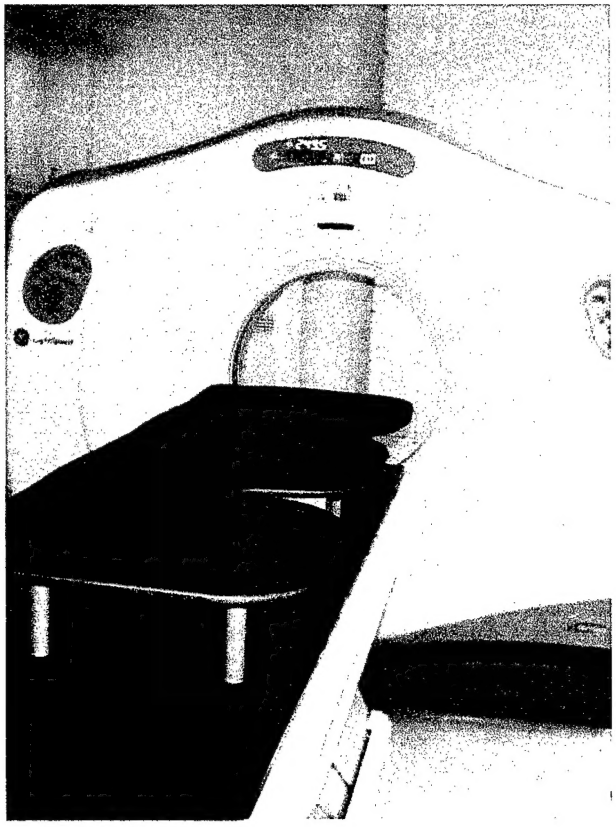

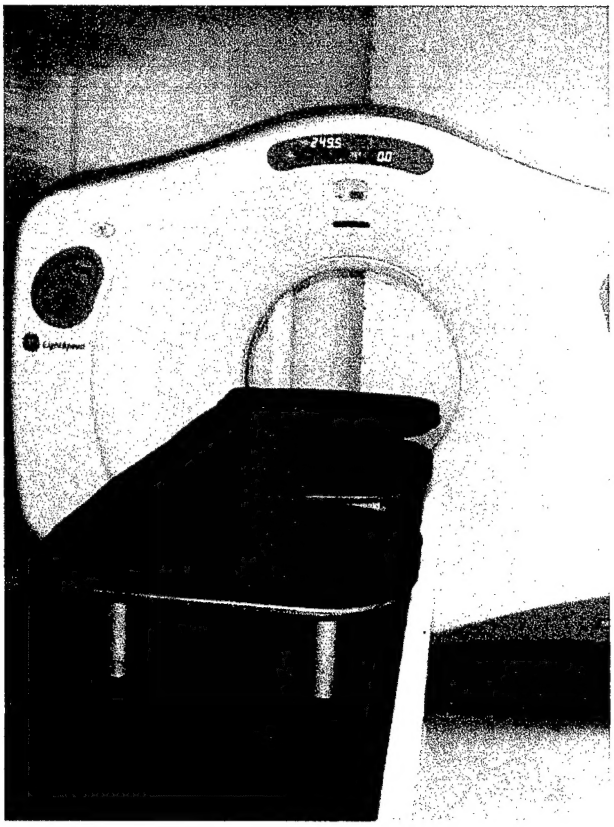
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